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Proposed Registration Decision PRD2016-19

# Octhilinone

*(publié aussi en français)*

**28 July 2016**

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-0878 (print)
1925-0886 (online)

Catalogue number: H113-9/2016-19E (print version)
H113-9/2016-19E-PDF (PDF version)

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# Overview

## Proposed Registration Decision for Octhilinone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Acticide OIT Technical Industrial Microbicide and Thor Acticide 45 Mildewcide, containing the technical grade active ingredient octhilinone, to provide protection of freshly treated wood against mold and mildew growth for a period of several months.

Octhilinone is currently registered as a mildewcide for a number of materials including caulks, sealants, adhesives, plastic and leather.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Acticide OIT Technical Industrial Microbicide and Thor Acticide 45 Mildewcide.

## What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on octhilinone, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on octhilinone, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

## What Is Octhilinone?

Octhilinone is a biocide currently registered as a preservative to prevent the growth of mold and mildew on a large number of materials ranging from paints and coatings to leather. It functions by inhibiting several specific enzymes, which results in the death of the microorganisms. The proposed use for octhilinone is as a mildewcide for wood freshly-treated with copper azole wood preservative.

## Health Considerations

### Can Approved Uses of Octhilinone Affect Human Health?

**Thor Acticide 45 Mildewcide, containing octhilinone, is unlikely to affect your health when used according to label directions.**

Potential exposure to octhilinone may occur when handling and applying the product or through contact with materials (wood) containing the product as a preservative. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

In laboratory animals, the active ingredient octhilinone was of moderate to high acute toxicity by the oral route, of slight acute toxicity by the dermal and inhalation routes, and corrosive to the eyes and skin. Octhilinone also caused an allergic skin reaction. Consequently, the hazard signal words "DANGER – POISON, CORROSIVE TO EYES AND SKIN, POTENTIAL SKIN SENSITIZER" are required on the label for the Acticide OIT Technical Industrial Microbicide.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The end-use product, Thor Acticide 45 Mildewcide, was of high acute toxicity via the oral route, of low acute toxicity via the dermal route, and of slight acute toxicity via inhalation. It was severely irritating to the skin and was considered corrosive to eyes. Thor Acticide 45 Mildewcide also caused an allergic skin reaction. Consequently, the hazard signal words "DANGER – POISON, CORROSIVE TO EYES, SEVERE SKIN IRRITANT, POTENTIAL SKIN SENSITIZER" are required on the label for the end-use product.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of octhilinone to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment were decreased growth, organ weight changes (increases in adrenal gland and heart weight), and irritation of the respiratory tract. There was no indication that the young animal was more sensitive than the adult animal. The risk assessment protects against these and any other potential effects by ensuring that the level of exposure to humans is well below the lowest dose at which these effects occurred in animal tests.

**Risks in Residential and Other Non-Occupational Environments**

**Estimated risks for non-occupational exposure are not of concern provided that directions specified on the label are followed.**

Residential exposure to individuals contacting wood products treated with octhilinone is not expected to result in health risks of concern when Thor Acticide 45 Mildewcide is used according to label directions.

**Occupational Risks from Handling Thor Acticide 45 Mildewcide**

**Occupational risks are not of concern when Thor Acticide 45 Mildewcide is used according to the proposed label directions, which include protective measures.**

A risk assessment conducted for individuals handling Thor Acticide 45 Mildewcide and wood treated with Thor Acticide 45 Mildewcide indicated that risks are not of health concern when the product is used according to label directions.

Pesticide applicators mixing, loading and applying Thor Acticide 45 Mildewcide can come in direct contact with octhilinone on the skin or through inhalation. Therefore, the label specifies that workers must wear full-face protection, chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gauntlets (long sleeved gloves), socks and chemical-resistant footwear when handling the concentrate or dilute solution, when opening treating cylinder doors, and during cleaning, maintenance and repair activities on storage vessels and treating cylinders. In addition, workers must wear a respirator with a NIOSH-approved organic vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides, when handling the concentrate, when handling the dilute solution in poorly ventilated areas, when opening treating cylinder doors and during cleaning, maintenance and repair activities on storage vessels or treating cylinders.

There is potential for exposure to workers handling wood after treatment. To minimize exposure to these workers, the label specifies that workers must wear chemical-resistant coveralls over long-sleeved shirt and long pants, goggles or face shield, chemical-resistant gauntlets (long sleeved gloves), and chemical-resistant footwear when there is a potential of getting wet by the preservative solution, when moving loads and handling freshly treated wood. For other activities that involve working under dry conditions, a long-sleeved shirt, long pants, chemical-resistant gloves, chemical goggles and chemical-resistant footwear are required.

## Environmental Considerations

### What Happens When Octhilinone Is Introduced Into the Environment?

**When used according to the label directions, octhilinone is not expected to pose risks of concern to the environment.**

Octhilinone can enter the environment by moving out of treated wood when in contact with water. Once in the terrestrial environment, octhilinone binds to soil particles and has a low potential for moving through soil. Octhilinone is not expected to enter saltwater aquatic systems as wood treated with octhilinone is not to be used in or near saltwater. Octhilinone is non-persistent in soil and freshwater aquatic systems as it transforms in the presence of both microorganisms and light. In freshwater aquatic systems, octhilinone will move from the water column into the sediment where it is expected to degrade. Residues of octhilinone are not expected to be found in air due to its low tendency to vaporize and are not expected to accumulate in the tissues of organisms or in the environment. Octhilinone does not form any significant breakdown products in the environment.

Under controlled laboratory conditions, octhilinone can be toxic to some non-target species such as birds, small wild mammals, aquatic invertebrates, fish and algae. When octhilinone is used according to the label directions, it is expected to pose negligible risk to the organisms listed above and the resulting environmental risk is considered to be acceptable. Standard precautionary environmental hazard statements are specified on the label to minimize possible environmental impacts.

## Value Considerations

### What Is the Value of Thor Acticide 45 Mildewcide?

**Thor Acticide 45 Mildewcide provides protection of freshly treated wood against mold and mildew growth for a period of several months.**

Thor Acticide 45 Mildewcide, when applied to the treatment solution of aqueous-based copper azole wood preservatives, is capable of providing protection from mold and mildew to the freshly treated wood for a period of up to six months.

## Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Thor Acticide 45 Mildewcide to address the potential risks identified in this assessment are as follows.

### Key Risk-Reduction Measures

#### Human Health

Because there is a concern with users coming into direct contact with octhilinone on the skin or through inhalation, workers must wear full-face protection, chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gauntlets (long sleeved gloves), socks and chemical-resistant footwear when handling the concentrate or dilute solution, when opening treating cylinder doors, and during cleaning, maintenance and repair activities on storage vessels and treating cylinders. In addition, workers must wear a respirator with a NIOSH-approved organic vapour-removing cartridge with a prefilter approved for pesticides, or a NIOSH-approved canister approved for pesticides, when handling the concentrate, when handling the dilute solution in poorly ventilated areas, when opening treating cylinder doors and during cleaning, maintenance and repair activities on storage vessels or treating cylinders. Workers must wear chemical-resistant coveralls over long-sleeved shirt and long pants, goggles or face shield, chemical-resistant gauntlets, and chemical-resistant footwear when there is a potential of getting wet by the preservative solution, when moving loads and handling freshly treated wood. For other activities that involve working under dry conditions, a long-sleeved shirt, long pants, chemical-resistant gloves, chemical goggles and chemical-resistant footwear are required.

#### Environment

To protect sensitive aquatic species, precautionary label statements identifying environmental hazards and preventing the use of treated wood in and near marine/estuarine environments are required on the product labels.

## Next Steps

Before making a final registration decision on octhilinone, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

## Other Information

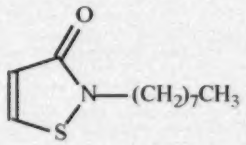
When the PMRA makes its registration decision, it will publish a Registration Decision on octhilinone (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

# Science Evaluation

## Octhilinone

## 1.0 The Active Ingredient, Its Properties and Uses

### 1.1 Identity of the Active Ingredient

| | |
|---|---|
| **Active substance** | Octhilinone |
| **Function** | Material Preservative |
| **Chemical name** | |
| **1. International Union of Pure and Applied Chemistry (IUPAC)** | 2-octyl-1,2-thiazol-3(2*H*)-one<br>Or<br>2-octylisothiazol-3(2*H*)-one |
| **2. Chemical Abstracts Service (CAS)** | 2-octyl-3(2*H*)-isothiazolone |
| **CAS number** | 26530-20-1 |
| **Molecular formula** | $C_{11}H_{19}NOS$ |
| **Molecular weight** | 213.34 |
| **Structural formula** |  |
| **Purity of the active ingredient** | 98.0% |

### 1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

**Technical Product – Acticide OIT Technical Industrial Microbicide**

| Property | Result |
|---|---|
| Colour and physical state | Deep yellow liquid |
| Odour | Mild |
| Melting range | N/A |
| Boiling point or range | 120°C |
| Density | 1.03 g/cm$^3$ at 20°C |
| Vapour pressure | 4.9 mPa at 25°C |

| Property | Result |
|---|---|
| Ultraviolet (UV)-visible spectrum | not expected to absorb at $\lambda > 300$ nm |
| Solubility in water | 0.525 g/L at 22°C |
| Solubility in organic solvents | Solvent — Solubility (g/L)<br>Methanol — >800<br>Toluene — >800<br>Ethyl acetate — >900<br>Hexane — 64 |
| *n*-Octanol-water partition coefficient ($K_{OW}$) | log $K_{OW}$ = 2.45 |
| Dissociation constant (p$K_a$) | N/A |
| Stability (temperature, metal) | Stable |

**End-Use Product – Thor Acticide 45 Mildewcide**

| Property | Result |
|---|---|
| Colour | Yellow |
| Odour | Mild |
| Physical state | Liquid |
| Formulation type | Solution |
| Guarantee | 45% |
| Container material and description | HDPE barrels, 50-200 kg |
| Density | 1.03 g/mL |
| pH of 1% dispersion in water | N/A |
| Oxidizing or reducing action | It may be deactivated by ammonia and amines at high pH. Avoid contact with strong oxidizing or reducing agents. |
| Storage stability | Stable for 1 year stored at room temperature. |
| Corrosion characteristics | No corrosion to the HDPE container stored at room temperature for 1 year. |
| Explodability | No explosive components. |

### 1.3 Directions for Use

Thor Acticide 45 Mildewcide, tank mixed with copper azole wood treatment solution, is recommended for the protection of freshly treated wood from mold and mildew degradation at a concentration of up to 0.55 kg Thor Acticide 45 Mildewcide per 1000 litres of treating solution (250 ppm octhilinone). At this level, adequate protection against mold and mildew growth on freshly treated wood may be expected for 6 months.

### 1.4 Mode of Action

Octhilinone is a biocide that functions by inhibiting several specific enzymes, thus disrupting central metabolic pathways such as cellular respiration and electron transport chain, from which most of the energy driving metabolism is derived. Cell death occurs after several hours of contact from the progressive loss of protein thiol groups.

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Acticide OIT Technical Industrial Microbicide have been validated and assessed to be acceptable for the determinations.

### 2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in Thor Acticide 45 Mildewcide has been assessed to be acceptable.

### 2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with mass spectrometry (HPLC-MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in animal matrices and environmental media. Methods for residue analysis are summarized in Table 1 of Appendix I.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

Acticide OIT Technical Industrial Microbiocide contains the active ingredient octhilinone or OIT. Octhilinone belongs to the isothiazolone class of chemicals.

A detailed review of the toxicological database for octhilinone was conducted. An extensive data package is available for octhilinone, with studies satisfying the majority of the toxicology data requirements. The purity of test material used in the toxicology studies varied. Doses were corrected for purity in those studies in which it was reported that the test material purity was low. Information contained in a Reregistration Eligibility Decision (RED) released in 2007 by the United States Environmental Protection Agency was also taken into consideration.

Studies conducted with another isothiazolinone, Kathon 886 Technical Microbiocide, which is a 3:1 mixture of 5-chloro-2-methyl-4-isothiazolin-3-one (IST) and 2-methyl-4-isothiazolin-3-one (ISL), were used to satisfy some of the data requirements for octhilinone. These studies included a 90-day inhalation toxicity study in the rat and a 2-year drinking water study in the rat. In order to assess the validity of this approach, an examination of the Kathon 886 database was undertaken and the toxicology profiles for Kathon 886 and octhilinone were compared. The available data indicated

that Kathon 886 and octhilinone produced a similar spectrum of toxicological effects, and that Kathon 886 was generally of comparable or higher toxicity than octhilinone; therefore, the studies conducted with Kathon 886 were considered acceptable to satisfy the respective data requirements.

Overall, the scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to octhilinone. Most of the core mammalian toxicity studies are considered acceptable by current standards, and were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. Although several studies were conducted before the implementation of Good Laboratory Practices, they were considered to contain scientifically valid information.

In acute toxicity testing, octhilinone was of moderate toxicity via the oral route in rats and of high toxicity via the oral route in rabbits. It was slightly toxic via the dermal route in rabbits and the inhalation route in rats, corrosive to the eye in rabbits, and sensitizing to the skin of mice in a local lymph node assay. Due to the known corrosive nature of octhilinone, the requirement for dermal irritation testing was waived. In supplemental studies with human volunteers, there was evidence of dermal sensitization following repeated dermal exposure to patches containing 1% octhilinone, as well as following repeated exposure of skin to octhilinone vapours. Human volunteers did not, however, exhibit a sensitization response following dermal exposure to cloth treated with 0.001% or 0.005% octhilinone.

In rats, the end-use product, Thor Acticide 45 Mildewcide, was demonstrated to be of high acute toxicity via the oral route, of low acute toxicity via the dermal route, and of slight acute toxicity via inhalation. In the rabbit, it was shown to be severely irritating to the skin. The requirement for an eye irritation study was waived, and the end-use product was considered to be corrosive to the eye. It also tested positive for dermal sensitization in a maximization study with guinea pigs at a concentration as low as 0.5%.

The absorption, distribution, metabolism and excretion of radiolabelled octhilinone, 2-n-octyl-4-[4,5-$^{14}$C]isothiazolin-3-one, following oral dosing was investigated in rats. Overall, there were no significant differences in the metabolic profile between males and females, or between single low and repeated low dosing scenarios. Approximately 65-75% of the administered dose (AD) was absorbed. Absorption was rapid following the administration of a single low dose, with the maximum concentration of radioactivity detected in plasma at 1 hour post-dosing. Slower absorption was evident following administration of a single high dose, with maximum plasma levels detected at 8 or 24 hours post-dosing. The maximum plasma concentration was only 3-5 times higher in high dose animals than in the low dose group, but the dose-normalized area under the curve (AUC) was generally similar among all dose groups.

Elimination of administered radioactivity occurred primarily via urine (44-51% of the AD), followed by feces (23-29% of the AD) and bile (19-20% of the AD). Minimal radioactivity was eliminated via expired air. Following administration of the low dose, the majority of the radioactivity was excreted during the first 24 hours, whereas the rate of excretion was somewhat slower following administration of the high dose, with the majority of radioactivity being excreted during the first 48 hours. Very little radioactivity (less than 3% of the AD) was retained in tissues at 96 hours after dosing. The radioactivity was widely distributed, with highest levels detected in the liver and kidney.

Octhilinone was extensively metabolized as no parent compound was detected in excreta. In urine samples, ten metabolites were identified, of which four were major (comprising more than 5% of the AD). In fecal samples, five metabolites were identified, two of which were major, while four metabolites were identified in bile, all of which were minor.

The biotransformation of octhilinone occurred via cleavage of the isothiazolinone ring through nucleophilic attack on the sulfur-nitrogen bond with consequent loss of the sulfur atom; oxidation at the isothiazolinone ring, either at the sulfur atom or at the double bond or within the n-octyl chain; and truncation at the alkyl chain. Phase II metabolism was also observed as glucuronidation, glutathione conjugation and N-acetylation.

Repeated-dose dietary toxicity studies were conducted with octhilinone in rats and dogs. Adverse effects in rats were limited to decreased body weight and body weight gain, as well as clinical signs and pathological lesions associated with irritation of the gastrointestinal tract. No adverse effects attributable to treatment were observed in dogs fed diet containing octhilinone for 90 days. Reduced palatability of the test diet limited the dose levels administered to dogs. The mixing of octhilinone with rodent or canine diet resulted in relatively low analytical recovery. Recovery was concentration-dependent, with lower recovery of test material from test diets with lower target concentrations of octhilinone. This lower recovery was presumed to be due to the reaction of octhilinone with sulfur-containing compounds in the diet and/or the irreversible binding of octhilinone to components in the diet. Binding of octhilinone to proteins in the diet would signify the opening of the isothiazolinone ring, resulting in a reduction in the amount of octhilinone available to exert toxicological effects. The administered doses in these studies were therefore corrected to account for this low analytical recovery.

Octhilinone has been tested in two 90-day dermal toxicity studies in rats, only one of which was available to the PMRA for review. In the study available to the PMRA, signs of dermal irritation were evident beginning at the mid-dose, with systemic toxicity in the form of reduced body weights and body weight gain in males, as well as increased adrenal gland and heart weights in females, occurring at the high dose. In the other 90-day dermal toxicity study in rats, summarized in the United States Environmental Protection Agency (USEPA) Reregistration Eligibility Decision (RED), dermal irritation occurred at all dose levels, including those that were much lower than the dose levels tested in the aforementioned study. In addition to the irritation, systemic toxicity included decreases in hemoglobin, hematocrit, red blood cells, albumin, glucose, and total protein in females, and decreases in body weight and body weight gain, increased alkaline phosphatase levels and decreased triglycerides in males. Although the NOAEL for systemic toxicity established by the USEPA was lower than that established in the first study, the USEPA did question the biological significance of the hematology and clinical chemistry changes in view of the low magnitude of the changes as well as their occurrence in only one sex. It was also noted in the USEPA RED that test sites were not occluded after dose administration. Overall, there was greater confidence in the results from the first 90-day dermal toxicity study from the perspective of hazard identification and risk assessment.

A 90-day inhalation toxicity study in rats conducted with octhilinone was available. In a Kathon 886 90-day inhalation toxicity study, slight nasal cavity irritation was observed at an exposure concentration that did not elicit systemic toxicity. Systemic effects in the form of decreased body weight and body weight gain, lymphoid hyperplasia of the lymph node, and organ weight changes

were only observed at the highest exposure concentration. Signs of both nasal irritation and systemic toxicity were noted at lower exposure concentrations with Kathon 886 than with octhilinone. In the 90-day inhalation toxicity study conducted with octhilinone, decreases in body weight and body weight gain were noted at the same exposure level that produced clinical signs and pathological lesions indicative of irritation of the upper respiratory tract. The potential for octhilinone to produce upper airway irritation was evaluated in a supplemental study conducted in mice.

A full battery of genotoxicity studies was available for octhilinone. Bacterial gene mutation assays, in vitro mammalian gene mutation assays, in vitro and in vivo unscheduled DNA synthesis assays and an in vivo micronucleus assay were all negative. An in vitro chromosomal aberration study in Chinese hamster ovary cells did indicate clastogenicity, but only at cytotoxic concentrations, and negative results were obtained in a second supplemental in vitro chromosomal aberration assay in human lymphocytes and in a supplemental in vivo chromosomal aberration assay. Overall, octhilinone was not considered to be genotoxic.

For the assessment of potential chronic toxicity and carcinogenicity of octhilinone, a 2-year drinking water study in rats conducted with Kathon 886 was considered an appropriate surrogate. Reduced body weight, body weight gain and food consumption as well as various signs of irritation in the stomach were observed in both sexes. Increased urinary specific gravity was also noted at the same dose level but was deemed secondary to reduced water consumption. No evidence of carcinogenicity was noted. An acceptable oncogenicity study in a second rodent species was not available for either octhilinone or Kathon 886. However, the carcinogenic potential of octhilinone was considered to be low on the basis of the negative results of the 2-year drinking water study in rats conducted with Kathon 886 and the overall negative genotoxicity profile.

The toxicology database for octhilinone did not allow for an assessment of durational effects. However, the toxicology database for Kathon 886 provided evidence that the toxicity of Kathon 886 increased with prolonged duration of dosing.

In a 2-generation reproductive toxicity study, rats were exposed to octhilinone via the diet. As with the repeated-dose dietary studies discussed above, the administered doses were corrected for low analytical recovery. Effects in offspring were limited to reductions in body weight and body weight gain during the latter part of the lactation phase, and decreases in spleen and thymus weight. These effects were noted at the highest dose tested, which also elicited parental toxicity in the form of reduced body weights and body weight gains in males, decreased body weight during lactation and organ weight changes in females, and stomach irritation in both sexes. Potential treatment-related changes in reproductive parameters were noted at the high dose only and included reduced ovarian weight in both generations, an increased incidence of epithelial mucification of the vagina in F1 animals (signifying a delayed return to a normal cyclical epithelium), and an increase in the number of primordial follicles. Since vaginal histology was not examined, nor were ovarian follicle counts determined for female rats from the low and mid dose groups, a NOAEL for reproductive toxicity in female rats could not be established.

In assessing the level of concern for this missing information, it was noted that, despite the effects on female reproductive parameters at the high dose in this study, there was no effect on estrous cycle, fertility or fecundity, nor were there any effects on the reproductive parameters that were assessed in male rats. Further, the endpoints selected for risk assessment afford an additional margin to the Lowest Observed Adverse Effects (LOAEL) for reproductive toxicity in females.

Two rat gavage developmental toxicity studies were available. In a study in which octhilinone was administered in corn oil, no adverse effects on maternal animals or fetuses were evident up to the highest dose tested. When octhilinone was administered in a propylene glycol/aqueous methylcellulose vehicle, maternal toxicity was evident at a dose that was lower than the highest dose tested in the previous study. This maternal toxicity manifested as decreased body weight and body weight gain, salivation, and the death of one animal. However, no developmental toxicity was apparent. In a gavage developmental toxicity study in rabbits, in which octhilinone was administered in a propylene glycol/aqueous methylcellulose vehicle, maternal animals exhibited significant body weight loss during dosing as well as anorexia and reduced fecal output, resulting in abortions in some animals. Reduced fetal body weights were recorded. All of these effects occurred at the highest dose tested. Results from a dose range-finding study conducted in non-pregnant rats, in which octhilinone was administered via gavage in corn oil, demonstrated that the pregnant animal was not more sensitive than the non-pregnant animal.

Results of the toxicology studies conducted on laboratory animals with octhilinone and its associated end-use product, Thor Acticide 45 Mildewcide, are summarized in Tables 2 and 3 of Appendix I. The toxicology endpoints for use in the human health risk assessment are summarized in Table 4 of Appendix I.

**Incident Reports**

Since 26 April 2007, registrants have been required by law to report incidents to the PMRA that include adverse effects to Canadian health or the environment. As of 25 September 2015, no human or domestic animal incidents involving the active ingredient octhilinone have been reported to the PMRA.

### 3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for octhilinone. The database contains the full complement of required studies including two developmental toxicity studies in rats, a developmental toxicity study in rabbits, and a 2-generation reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of fetuses or offspring compared to parental animals in the reproductive and prenatal developmental toxicity studies. No developmental toxicity was noted in rats, and abortions and reduced fetal body weight observed in the rabbit occurred in the presence of significant maternal body weight loss. In the rat reproductive toxicity study, reduced body weights and body weight gains noted in offspring during the latter part of the lactation period, as well as decreased spleen and thymus weight in weanling rats, occurred in the presence of maternal toxicity (stomach irritation, decreased body weight, organ weight changes). Overall, endpoints in the young were well-characterized and not considered serious in nature. On the basis of this information, the *Pest Control Products Act* factor was reduced to 1-fold.

### 3.2 Acute Reference Dose (ARfD)

An acute reference dose (ARfD) was not established as there are no food uses for octhilinone.

### 3.3 Acceptable Daily Intake (ADI)

An acceptable daily intake (ADI) was not established as there are no food uses for octhilinone.

### 3.4 Toxicological Endpoints

**Short- to Intermediate-Term Dermal**

For short- to intermediate-term dermal exposure scenarios, the No Observed Adverse Effect Level (NOAEL) of 25 mg/kg bw/day for systemic toxicity from the 90-day dermal toxicity study in rats was selected for use in risk assessment. Reduced body weights and body weight gains in males, and increased adrenal gland and heart weights in females, were observed at the Lowest Observed Adverse Effect Level (LOAEL) of 125 mg/kg bw/day. This study represented the appropriate route and duration of exposure for risk assessment.

The target Margin of Exposure (MOE) is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Use of the NOAEL of 25 mg/kg bw/day and the target MOE of 100 provides a margin in excess of 450-fold to the LOAEL of 114 mg/kg bw/day for reproductive effects in female rats in the 2-generation reproductive toxicity study.

**Long-Term Dermal**

For long-term dermal exposure scenarios, the NOAEL of 25 mg/kg bw/day for systemic toxicity from the 90-day dermal toxicity study in rats was selected for use in risk assessment. Reduced body weights and body weight gains in males, and increased adrenal gland and heart weights in females, were observed at the LOAEL of 125 mg/kg bw/day.

A long-term dermal toxicity study conducted with octhilinone was not available. Although a 2-year drinking water study with Kathon 886 was available, the 90-day dermal toxicity study was selected as it was conducted with the appropriate chemical (octhilinone as opposed to ISL and IST) and represented the relevant route of exposure.

The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as an additional 3-fold factor to extrapolate from a short-term to a long-term exposure scenario considering the evidence for increased toxicity with prolonged duration of dosing in the Kathon 886 toxicological database.

Use of the NOAEL of 25 mg/kg bw/day and the target MOE of 300 provides a margin in excess of 1400-fold to the LOAEL of 114 mg/kg bw/day for reproductive effects in female rats in the 2-generation reproductive toxicity study.

**Long-Term Inhalation**

For long-term inhalation exposure scenarios, the NOAEC of 0.64 $mg/m^3$ (equivalent to 0.17 mg/kg bw/day) from the 90-day inhalation toxicity study in rats conducted with octhilinone was selected for use in risk assessment. Reduced body weight and body weight gain, clinical signs, and nasal cavity lesions were observed at the LOAEC of 6.39 $mg/m^3$ (equivalent to 1.67 mg/kg bw/day).

A long-term inhalation toxicity study conducted with octhilinone was not available. Although a 2-year drinking water study with Kathon 886 was available, the 90-day inhalation toxicity study was selected as it was conducted with the appropriate chemical (octhilinone as opposed to ISL and IST) and represented the relevant route of exposure.

The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as an additional 3-fold factor to extrapolate from a short-term to a long-term exposure scenario considering the evidence for increased toxicity with prolonged duration of dosing in the Kathon 886 toxicological database.

Use of the NOAEC of 0.64 $mg/m^3$ (equivalent to 0.17 mg/kg bw/day) and the target MOE of 300 provides a margin in excess of 200,000-fold to the LOAEL of 114 mg/kg bw/day for reproductive effects in female rats in the 2-generation reproductive toxicity study.

**Non-Dietary Oral Ingestion (Children, Short- to Intermediate-Term)**

For the assessment of risk to children from non-dietary (incidental) oral ingestion, the NOAEL for maternal toxicity of 5 mg/kg bw/day from the gavage developmental toxicity study in the rat was selected. Salivation, reduced body weights and body weight gains, and the death of one maternal animal were observed at the LOAEL of 30 mg/kg bw/day.

Although these effects were observed in maternal animals, they are considered relevant endpoints in an assessment of risks to children and the available data did not suggest that pregnant animals were more sensitive than non-pregnant animals to the toxic effects from exposure to octhilinone.

The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

**Dermal Sensitization**

Because of the positive skin sensitization study findings, the well-known sensitization potential of isothiazolinones, and the use pattern for octhilinone, a sensitization risk assessment was deemed appropriate. A quantitative approach to the sensitization risk assessment was undertaken in light of the fact that a local lymph node assay study with octhilinone was available. An $EC_3$ of 0.46%, equivalent to 230 $\mu g/cm^2$, was established in the study and was considered appropriate for use in risk assessment.

The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability.

**Cancer Assessment**

Octhilinone is not considered to pose a carcinogenic hazard; therefore, a cancer risk assessment is not required.

## 3.5 Occupational and Residential Risk Assessment

### 3.5.1 Toxicological Endpoints

Occupational exposure to octhilinone is characterized as long-term in duration and is predominantly by the dermal and inhalation routes. Residential exposure to octhilinone from treated wood is characterized as short- to intermediate-term in duration; all individuals may be exposed by the dermal route and toddlers may be exposed via incidental oral ingestion from hand-to-mouth activities.

#### 3.5.1.1 Dermal Absorption

Dermal absorption data were not submitted for octhilinone. In addition, a dermal absorption factor is not required, since the toxicological endpoints relevant to dermal exposure are based on a dermal toxicity study.

### 3.5.2 Occupational Exposure and Risk

There is potential for exposure to workers in sawmills treating wood with Thor Acticide 45 Mildewcide and handling treated wood. Exposure to workers is expected to be long-term in duration and to occur primarily by the dermal and inhalation routes.

Dermal and inhalation exposure estimates for workers were generated from a surrogate passive dosimetry study conducted to monitor worker exposure associated with pressure-treatment of wood. The exposure estimates are based on workers wearing a long-sleeved shirt and long pants, socks and shoes (or tall rubber boots when workers were on the drip pad of the treatment plant).

The observational surrogate passive dosimetry study was designed to measure exposure to 23 workers in 5 sites in the United States involved with pressure-treatment of wood with an antimicrobial wood preservative. The workers were monitored conducting tasks 1) on the drip pad, 2) at/near the cylinder door and drip trench, and 3) in the treatment control room, analytical laboratory, and tank farm. Workers were categorized as treatment operators (TOs; n = 11) and wood handlers (WHs; n = 12), although many workers were involved with both TO-related and WH-related activities during the monitoring event. All subjects wore a fresh cotton long-sleeved work shirt and fresh cotton long pants (outer dosimeter), fresh polypropylene socks (outer socks) and shoes. Most workers also wore chemical-resistant gloves (either heavy rubber gloves, exam gloves or both), except workers in Site A who wore leather gloves or no gloves at all. Some operators wore additional protective clothing: hard hats, tall rubber boots, goggles, respirator, and ear protection.

Dermal exposure was monitored using inner whole body dosimeters (cotton one-piece union suits worn under the work shirt and long pants), inner socks (worn under the outer socks), face/neck wipes, and hand wash samples. Inhalation exposure was monitored using a personal air sampling pump on the subject's belt, which pulled breathing-zone air through a sampling train constructed to permit the separation of particulate and vapour-phase active ingredient, and the partitioning of retained particulates into fractions reflecting the American Conference of Governmental Industrial Hygienists (ACGIH) particle-size criteria. The sampling train consisted of a polyurethane foam cylinder (PUF plug) inserted in an Institute of Occupational Medicine (IOM) sampler to retain the inhalable fraction. A quartz fibre filter was inside the IOM sampler cassette to retain the respirable fraction and part of the thoracic fraction. Tygon tubing connected the IOM sampler and the OSHA Versatile Sampler (OVS) tube, which retained any vapor-phase active ingredient.

The average replicate length was 454 minutes (7.6 hours). The target % of active ingredient (a.i.) in the treating solution ranged from 0.250 – 0.878% (average of 0.432%). The volume of treating solution used per work shift ranged from 3,526 (Site C) – 11,614 gallons (Site E). Test samples of the treating solutions were taken from the charges monitored, except for Site C. On average for each site, treating solution samples collected at Sites A, B, D, and E contained 69%, 64%, 89% and 80% of target a.i. levels, respectively, compared to those reported by on-site equipment in the charge reports. These results were used to calculate the weighted concentration of the treating solution of each work shift.

Total dermal exposure was calculated by summing the residues on inner dosimeters, inner socks, face/neck wipes, and hand wash samples. To calculate inhalation exposure, residues from air sampling matrices were divided by the pump flow rate and multiplied by the inhalation rate for light activity (16.7 L/min). To calculate air concentration, residues from air sampling matrices were multiplied by the pump flow rate (L/min) and sampling duration (min); results in µg/L were then converted to $mg/m^3$. To calculate inhalable inhalation exposure or air concentration, the sum of residues from all air sampling matrices was used; to calculate respirable inhalation exposure or air concentration, the sum of the residues on/in the air filter and OVS tube was used.

The dermal exposure values, inhalation exposure values, and air concentrations were normalized by the weighted concentration of the treating solution of the work shift corresponding to the replicate. Residues were corrected for site-specific field recoveries that were <95%. Residues less than the limit of quantitation (LOQ) were not corrected and were entered as ½ LOQ in calculations.

The results from hand washes of workers in Site A were not included in the statistical results of this study, since workers did not wear chemical-resistant gloves during the monitoring event.

Field fortification results were acceptable and the study had minor limitations. As such, arithmetic means of the unit exposures and air concentrations were considered appropriate for risk assessment purposes. Table 3.5.2.1 presents the arithmetic means of the total dermal unit exposures and inhalation unit exposures, as well as the unit air concentrations.

**Table 3.5.2.1 Arithmetic means of total dermal unit exposure, and inhalation unit exposures and air concentrations (inhalable and respirable)**

| Worker category | n | Unit exposure (µg/% a.i. in treating solution) | | | Unit air concentration ($mg/m^3$ /% a.i. in treating solution) | |
|---|---|---|---|---|---|---|
| | | Total dermal[a] | Inhalable | Respirable[b] | Inhalable | Respirable[b] |
| Treatment operators (TO) | 11 | 1265 | 29.23 | 11.45 | $3.99\times10^{-3}$ | $1.60\times10^{-3}$ |
| Wood handlers (WH) | 12 | 5467 | 138.28 | 17.22 | $1.77\times10^{-2}$ | $2.17\times10^{-3}$ |

[a] Total dermal unit exposures do not include the hand wash results from Site A (n = 2 from both TO and WH categories), since workers in Site A did not wear chemical-resistant gloves during the monitoring event.
[b] Due to the air sampling methodology used in this study, the calculated respirable unit exposures and air concentrations are potentially overestimations.

Dermal exposure was estimated by coupling the unit exposure values with the concentration of octhilinone in the treating solution containing Thor Acticide 45 Mildewcide. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

To assess inhalation risk, since it is uncertain which part of the respiratory tract may be affected by octhilinone, inhalable unit exposure and unit air concentration were used. Since the inhalation no observable adverse effect level (NOAEL) is expressed both as dose (mg/kg bw/day) and as air concentration ($mg/m^3$), both were used to assess inhalation risk and then compared. Inhalation exposure was estimated by coupling the unit exposure values with the concentration of octhilinone in the treating solution containing Thor Acticide 45 Mildewcide with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight. Air concentration was estimated by coupling the unit air concentration with the concentration of octhilinone in the treating solution containing Thor Acticide 45 Mildewcide.

Exposure estimates were compared to the toxicological endpoint (NOAELs or no observable adverse effect concentration [NOAEC]) to obtain the margin of exposure (MOE); the target MOE is 300. All calculated dermal and inhalation MOEs are above the target MOE of 300.

**Table 3.5.2.2 Dermal and Inhalation Exposure and Risk from the Use of Thor Acticide 45 Mildewcide to Workers in Wood Treatment Plants**

| DERMAL EXPOSURE AND RISK | | | | |
|---|---|---|---|---|
| **Worker category** | **Total dermal unit exposure (µg/% a.i.)** | **Treating solution concentration (% a.i.)** | **Dermal exposure (mg/kg bw/day)[a]** | **Calculated MOE[b]** |
| Treatment operators | 1265 | 0.025 | 0.000395 | 64,241 |
| Wood handlers | 5467 | | 0.00171 | 14,633 |
| **INHALATION EXPOSURE AND INHALATION RISK CALCULATED FROM EXPOSURE** | | | | |
| **Worker category** | **Inhalable unit exposure (µg/% a.i.)** | **Treating solution concentration (% a.i.)** | **Inhalation exposure (mg/kg bw/day)[c]** | **Calculated MOE[d]** |
| Treatment operators | 29.23 | 0.025 | $9.13\times10^{-6}$ | 18,611 |
| Wood handlers | 138.28 | | $4.32\times10^{-5}$ | 3934 |
| **AIR CONCENTRATION AND INHALATION RISK CALCULATED FROM AIR CONCENTRATION** | | | | |
| **Worker category** | **Inhalable unit air concentration ($mg/m^3$ / % a.i.)** | **Treating solution concentration (% a.i.)** | **Air concentration ($mg/m^3$)[e]** | **Calculated MOE[f]** |
| Treatment operators | 0.00399 | 0.025 | $9.98\times10^{-5}$ | 6416 |
| Wood handlers | 0.0177 | | $4.43\times10^{-4}$ | 1446 |

[a] Dermal exposure (mg/kg bw/day) = $\frac{\text{Total dermal unit exposure (µg/\% a.i.)} \times \text{Treating solution concentration (\% a.i.)}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$

[b] Based on NOAEL of 25 mg/kg bw/day, target MOE = 300

[c] Inhalation exposure (mg/kg bw/day) = $\frac{\text{Inhalable unit exposure (µg/\% a.i.)} \times \text{Treating solution concentration (\% a.i.)}}{80 \text{ kg bw} \times 1000 \text{ µg/mg}}$

[d] Based on NOAEL of 0.17 mg/kg bw/day, target MOE = 300

[e] Air concentration ($mg/m^3$) = Inhalable unit air concentration ($mg/m^3$ /% a.i.) × Treating solution concentration (% a.i.)

[f] Based on NOAEC of 0.64 mg/kg bw/day, target MOE = 300

Both dermal and inhalation exposure to octhilinone can result in similar effects (reduced body weight and body weight gain); thus, risks were combined. Inhalation MOEs calculated from air concentrations ($mg/m^3$) were used in the calculation of combined risk, since they were more conservative than those calculated from inhalation exposure (mg/kg bw/day). All calculated MOEs for combined risk are above the target MOE of 300.

**Table 3.5.2.3 Combined Risk from the Use of Thor Acticide 45 Mildewcide to Workers in Wood Treatment Plants**

| Worker category | Dermal MOE[a] | Inhalation MOE[b] | Combined MOE[c] |
|---|---|---|---|
| Treatment operators | 63,241 | 6416 | 5825 |
| Wood handlers | 14,633 | 1446 | 1316 |

[a] Calculated dermal MOEs from Table 3.4.2.4.

[b] Inhalation MOEs calculated from air concentrations ($mg/m^3$) from Table 3.4.2.2.

[c] Combined MOE = 1 / (1/Dermal MOE + 1/Inhalation MOE), target MOE = 300

As such, according to the risk assessment, health risk from exposure to octhilinone is not of concern when workers wear a long-sleeved work shirt, long pants, socks, and chemical-resistant gloves and chemical-resistant footwear, which was the personal protective equipment (PPE) worn by the workers in the surrogate study.

In addition, to protect workers from the acute toxicity of Thor Acticide 45 Mildewcide, workers must wear at minimum coveralls over a single layer, chemical-resistant gloves, socks and chemical-resistant footwear during mixing, loading, application, clean-up and repair, and protective eyewear during mixing and loading.

However, additional PPE is required for personnel who work with preservatives as per the "Recommendations for Design and Operation of Wood Preservation Facilities, 2013 Technical Recommendations Document (TRD)" which is enforced by Environment Canada. As such, the PPE statement on the Thor Acticide 45 Mildewcide label reflects the requirements based on the risk assessment, acute toxicity of Thor Acticide 45 Mildewcide and the TRD.

### 3.5.3 Residential Exposure and Risk Assessment

#### 3.5.3.1 Postapplication Exposure and Risk

Postapplication exposure can occur for adults and children through contact with the treated wood products. Adults can be exposed in scenarios, such as do-it-yourself construction of wood decks. Children can be exposed during activities such as crawling on wood decks and playing on wood playground equipment. Postapplication exposure from vacuum/pressure treated lumber is expected to be of short- to intermediate-term in duration; all individuals may be exposed by the dermal route and toddlers may be exposed via incidental oral ingestion from hand-to-mouth activities.

To estimate exposure to octhilinone from residues transferred from treated wood, chemical-specific transferable residue data were used. The transferable residue (wipe) study was designed to determine the amount of dislodgeable octhilinone residues from Jack Pine and Lodgepole Pine lumber vacuum/pressure treated (similar to what is done commercially) with a tank mix of Thor Acticide 45 Moldicide at 250 ppm octhilinone and a copper azole formulation at 0.2, 0.4 or 0.8% active ingredient. The wood was not weathered between treatment and sampling. Transferable residues were sampled on a single sampling day (40 – 45 days after treatment) using a wet wipe sampling method.

Transferable residues of octhilinone were shown to be higher in Jack Pine than in Lodgepole Pine, and in boards treated with lower concentrations of copper azole (0.2 – 0.4%) than in those treated with a higher concentration of copper azole (0.8%). As wood for above ground use (such as decks) are treated at lower concentrations of copper azole (minimum of 0.3%), transferable residues of octhilinone from boards treated with lower concentrations of copper azole were used for risk assessment.

In addition, samples were taken 40 – 45 days after treatment; however, treated wood could be in the consumer market and used before this period. Due to this major limitation, the highest transferable residue value for octhilinone was used to estimate exposure to people contacting wood treated with Thor Acticide 45 Mildewcide. The highest transferable residue value for octhilinone was 0.176 $\mu g/cm^2$ from one sample of Jack Pine lumber treated at 0.4% copper azole and 250 ppm octhilinone.

The postapplication risk assessment was conducted according to the 2012 USEPA Residential Standard Operating Procedures (SOP).

#### 3.5.3.1.1 Dermal Exposure

Dermal exposure from postapplication activity with pressure-treated wood was calculated with the following equation:

Dermal exposure (mg/kg bw/day) = SR * SA/BW * $F_{body}$ * TE

| | | |
|---|---|---|
| Where | SR | = Surface residue concentration (mg/cm$^2$) |
| | SA/BW | = Total body surface area to body weight ratio (cm$^2$/kg) |
| | $F_{body}$ | = Fraction of total body skin surface area that is unclothed |
| | TE | = Daily material-to-skin transfer efficiency (fraction/day) |

Surface residue concentration (SR) * daily material-to-skin transfer efficiency (TE) is equivalent to the transferable residue from the wood surface (TR), which is derived from the wipe study. As such, the dermal exposure for Thor Acticide 45 Mildewcide was calculated using the following equation:

Dermal exposure (mg/kg bw/day) = TR * SA/BW * $F_{body}$

| | | |
|---|---|---|
| Where | TR | = Transferable residue concentration (mg/cm$^2$) |
| | SA/BW | = Total body surface area to body weight ratio (cm$^2$/kg) |
| | $F_{body}$ | = Fraction of total body skin surface area that is unclothed |

Table 3.5.3.1 presents the dermal postapplication risk assessment from the use of Thor Acticide 45 Mildewcide on pressure-treated lumber. For all populations, calculated MOEs for dermal exposure were above the target MOE of 100.

**Table 3.5.3.1 Postapplication Dermal Exposure and Risk to Octhilinone from Lumber Pressure-Treated with Thor Acticide 45 Mildewcide**

| Population | Transferable Residue (mg/cm$^2$)[a] | Surface area / Body weight Ratio (cm$^2$/kg)[b] | Fraction of body exposed | Dermal exposure (mg/kg bw/day)[c] | Calculated MOE[d] |
|---|---|---|---|---|---|
| Adults | 0.000176 | 280 | 0.31 | 0.0153 | 1636 |
| Youth (11 <16 years) | 0.000176 | 280 | 0.31 | 0.0153 | 1636 |
| Children (1 <2 years) | 0.000176 | 640 | 0.31 | 0.0349 | 716 |

[a] Transferable residue = 0.176 µg/cm$^2$ from the wipe study = 0.000176 mg/cm$^2$
[b] Values from the 2012 USEPA Residential SOP
[c] Exposure = Transferable Residue × Surface area/Body weight Ratio × Fraction of body exposed
[d] Based on NOAEL = 25 mg/kg bw/day, target MOE = 100

#### 3.5.3.1.2 Dermal Sensitization

Octhilinone also has an $EC_3$ for dermal sensitization. As such, it was compared with the transferable residue from the wood surface, which was derived from the wipe study:

$$\text{Calculated MOE} = \frac{\text{Dermal sensitization } EC_3}{\text{TR from wipe study}} = \frac{230\ \mu g/cm^2}{0.176\ \mu g/cm^2} = 1310$$

There is no risk of concern for dermal sensitization through postapplication exposure to treated wood.

#### 3.5.3.1.3 Incidental Oral Exposure

Incidental oral exposure from postapplication activity with pressure-treated wood was calculated with the following equation:

$$\text{Exposure} = \frac{HR \times (F_M \times SA_H) \times (ET \times N_Replen) \times [1 - (1 - SE)^{(Freq_HtM/N_Replen)}]}{\text{Body weight}}$$

Where E = incidental oral exposure (mg/day)
HR = hand residue loading (mg/cm$^2$) = transferable residue
$F_M$ = fraction hand surface area mouthed / event (fraction/event)
$SA_H$ = surface area of one hand (cm$^2$)
ET = exposure time (hr/day)
N_Replen = number of replenishment intervals per hour (intervals/hour)
SE = saliva extraction factor (that is, mouthing removal efficiency)
Freq_HtM = number of hand-to-mouth contacts per hour (events/hour)

Table 3.5.3.2 presents the incidental oral postapplication risk assessment from the proposed use of Thor Acticide 45 Mildewcide on pressure-treated lumber. The calculated MOE for incidental oral exposure was above the target MOE of 100.

**Table 3.5.3.2 Postapplication Incidental Oral Exposure and Risk to Octhilinone from Lumber Pressure-Treated with Thor Acticide 45 Mildewcide**

| Population | TR (mg/cm$^2$)[a] | $F_M$ (fraction/ event)[b] | $SA_H$ (cm$^2$)[b] | ET (hr/day)[b] | N_Replen (intervals/ hour)[b] | SE[b] | Freq_ HtM (events/ hour)[b] | Exposure (mg/kg bw/day)[c] | MOE[d] |
|---|---|---|---|---|---|---|---|---|---|
| Children (1 <2 years) | 0.000176 | 0.13 | 150 | 1.5 | 4 | 0.48 | 13.9 | 0.00162 | 3086 |

[a] TR = transferable residue = 0.176 µg/cm$^2$ from the wipe study = 0.000176 mg/cm$^2$
[b] $F_M$ = fraction hand surface area mouthed / event, $SA_H$ = surface area of one hand, ET = exposure time, N_Replen = number of replenishment intervals per hour, SE = saliva extraction factor, Freq_HtM = number of hand-to-mouth contacts per hour (events/hour)
Default values from the 2012 USEPA Residential SOPs were used for these parameters.
[c] $\text{Exposure} = \frac{\text{Transferable residue} \times (F_M \times SA_H) \times (ET \times N_Replen) \times [1 - (1 - SE)\ \text{^}\ (Freq_HtM/N_Replen)]}{\text{Body weight}}$
Body weight = 11.4 kg for children (1<2 years) from the 2012 USEPA Residential SOPs
[d] Based on NOAEL = 5 mg/kg bw/day, target MOE = 100

Both dermal and incidental oral exposure can result in similar effects (reduced body weight and body weight gain); as such, the risk from both routes of exposure were combined for children 1<2 years old (Table 3.5.3.3). The combined MOE was above the target MOE of 100.

**Table 3.5.3.3 Postapplication Combined Exposure and Risk to Octhilinone from Lumber Pressure-Treated with Thor Acticide 45 Mildewcide**

| Population | Dermal MOE[a] | Incidental Oral MOE[b] | Combined MOE[c] |
|---|---|---|---|
| Children (1<2 years) | 716 | 3086 | 581 |

[a] From Table 3.5.3.1
[b] From Table 3.5.3.2
[c] Combined MOE = 1 / (1/Dermal MOE + 1/Incidental Oral MOE)

From dermal exposure to adults and youth, and from combined dermal and incidental oral exposure to children, all calculated MOEs were above the target MOE of 100. As such, for all populations, postapplication health risk from lumber pressure-treated with Thor Acticide 45 Mildewcide is not of concern.

### 3.5.3.2 Bystander Exposure and Risk

This is a commercial product used in commercial settings, and bystander exposure is considered negligible. Therefore, health risk to bystanders is not of concern.

### 3.6 Aggregate Exposure and Risk

Octhilinone is currently registered for other uses, which lead to potential exposure to adults and children, including treatment of carpets, floors, mattresses and clothing. However, the likelihood of co-occurrence of postapplication exposure to these treated materials and treated wood is minimal. As such, an aggregate postapplication risk assessment was not conducted.

## 4.0 Impact on the Environment

### 4.1 Fate and Behaviour in the Environment

Octhilinone enters the soil through leaching from treated wood used for construction of outdoor structures due to direct contact with rain water. A study on leaching of wood blocks of Lodgepole pine indicated a maximum leaching rate during the first six hours of being submersed in water followed by a declining rate until the end of the 14-day study (Table 8 of Appendix I). No field data are available to confirm the leaching behaviour of octhilinone in the environment. A laboratory study indicated that it strongly adsorbs to soil particles and, as such, is expected to have a low mobility in soil and thus, has low potential to leach and contaminate groundwater. Although phototransformation in soil can occur, it is not expected to be a significant route of dissipation. Octhilinone is non-persistent in soil; aerobic biotransformation is the main transformation pathway and no major transformation products were observed under aerobic conditions. Its behaviour under anaerobic conditions is unknown.

Octhilinone enters aquatic systems through leaching from treated wood used in the vicinity of water such as docks, walkways, board walks, etc., due to direct contact with water (for example, rain, waves, splashes). It can also enter the aquatic environment through runoff from structures such as decks, patios, and fencing. Wood treated with octhilinone is not to be used in or near marine/estuarine environment; therefore octhilinone is not expected to enter saltwater aquatic systems. Octhilinone is very soluble in water and is stable to hydrolysis. Biotransformation is a

major route of dissipation of octhilinone in water. It is non-persistent with no major transformation products observed under aerobic conditions. Octhilinone is expected to adsorb to sediments where it is expected to be non-persistent.

Laboratory studies indicated that octhilinone is not likely to volatilize from moist soil, water surfaces or wood, and is unlikely to bioconcentrate or bioaccumulate in organisms. The environmental fate data for octhilinone are summarized in Table 5 of Appendix I.

### 4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide in the environment.

EECs of octhilinone are based on selected exposure scenarios, developed from the OECD Emission Scenario Document for wood preservatives. Scenario selection was based on the following considerations:

- Octhilinone is to be used in conjunction with copper-azole wood preservatives, and, as such, will only be applied in vacuum/pressure treatment facilities.

- As octhilinone is not expected to volatilize, and it is expected to rapidly degrade in air, EECs in air are expected to be negligible. EECs for this compartment are not required.

- Octhilinone enters the terrestrial environment through leaching from treated wood used for construction of outdoor structures. Terrestrial organisms may be exposed to octhilinone either by direct contact with treated wood or indirectly, by contact with the leachate of the treated wood or with soil, water or food source contaminated via surface runoff/drainage. In general, for wood preservatives, exposure of non-target organisms in the terrestrial environment is expected to be low. As octhilinone is expected to rapidly dissipate from soil and water, exposure of terrestrial organisms is expected to be negligible. No further assessment of the risk to terrestrial organisms is required.

- Octhilinone enters the aquatic environment through leaching from treated wood used in the vicinity of water, such as docks, walkways, board walks, etc. due to direct contact with water (for example, rain, waves, splashes). It can also enter the aquatic environment through runoff from structures in the terrestrial environment, such as decks, patios, and fencing. Label restrictions preventing the use of copper-azole treated wood in and near marine and estuarine environments limits the potential for octhilinone to reach these environments.

The exposure scenarios for freshwater organisms therefore considers direct input to a (generic) aquatic system from in situ uses of wood treated with octhilinone (for example, dock, bridge, walkway; scenario 2), as well as surface runoff from both in-service uses (for example, decks and

fences; scenario 3) and storage at treatment facilities (that is, storage of treated wood in open yards at vacuum/pressure treatment facilities; scenario 1). No exposure scenario for marine and estuarine organisms was considered, as treated wood is not to be used in and near marine and estuarine environments. Details for all exposure scenarios are presented in Table 7 (Appendix I).

EECs are derived from the specific scenario parameters identified in Table 7 (Appendix I) and from the flux of active ingredient estimated from leaching data (Table 8 of Appendix I). For each scenario, EECs are calculated on a daily basis, considering the aquatic biotransformation half-life of octhilinone, for a period of time equal to the expected service-life of the treated wood, or until the total amount of active ingredient present in wood has leached, whichever comes first.

For each scenario, three EEC values are reported (Table 9 of Appendix I): the EEC at the end of the first day after installation/immersion of the wooden structure, a longer-term EEC, and the maximum EEC expected for the entire service-life of the treated wood. The moment when the maximum EEC is expected to occur (in terms of days after installation/immersion of the wooden structure) is also reported. A single value is presented as longer-term EEC due to the fact that, when rounded to a single digit, EECs calculated on day 14 after installation/immersion of the wooden structure, as well as for each day of the rest of the service life of the treated wood, are identical.

Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. A summary of the available toxicity data is presented in Table 6, Appendix I. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (that is, protection at the community, population, or individual level).

For characterizing acute risk, acute toxicity values (for example, $LC_{50}$, $LD_{50}$, and $EC_{50}$) are divided by an uncertainty factor. The uncertainty factor is used to account for differences in inter- and intra-species sensitivity as well as varying protection goals (for example, community, population, individual). Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (for example, 10 for fish, 2 for aquatic invertebrates). The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level (that is, feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. When assessing chronic risk, the NOEC or NOEL is used and an uncertainty factor is not applied.

A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the RQ is then compared to the level of concern. If the screening level RQ is below the LOC (LOC=1 for aquatic assessments), the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then further characterization of the risk is required. To help in characterizing the risk, the number of days during which the RQ is greater that the LOC is reported (Days at RQ > 1).

**Freshwater Invertebrates:** The risk assessment indicated that the RQ values for acute toxicity to *D. magna* did not exceed the LOC for either surface runoff from a lumber storage area at a treatment facility (Table 9, Appendix I) or leaching from in-service wood directly into a generic

freshwater environment (that is, a pond; Table 10, Appendix I). The RQ value did, however, exceed the LOC when considering chronic exposure to runoff from in-service terrestrial uses (for example, decks and fences; Table 11, Appendix I). Based on this runoff scenario, the RQ exceeded the LOC after the first rain event following installation of the wooden structure, reaching a maximum slightly above the LOC on day two, and falling below the LOC by day eight. This result is based on the conservative assumption that 50% of the pesticide leached reaches the aquatic environment following an average rain pattern, and that both structures (fence and deck) are installed simultaneously or consecutively with no rain events occurring before the end of installation. RQ would be less if rain occurs during the course of installation, causing only a fraction of the wood area to be exposed to rain. RQ would also be less if the first rain events following the installation are less frequent than average, allowing for greater biotransformation of the active ingredient between rain events. Considering this information, the overall conclusion is that the probability of freshwater invertebrates being exposed to octhilinone at concentrations causing effects, when used as a heavy duty wood preservative, is low.

**Freshwater Fish and Amphibians:** The risk assessment indicated that the RQ values for acute toxicity did not exceed the LOC for fish, for all acute exposure scenarios (Table 9, Table 10 and Table 11, Appendix 1). The risk to aquatic life stages of amphibians was assessed based on the generic freshwater environment scenario, using the most sensitive fish toxicity values as a surrogate endpoint (that is, based on the rainbow trout acute toxicity study). The RQ for acute exposure of amphibians to octhilinone did not exceed the LOC (Table 10, Appendix 1).

**Freshwater Plants (vascular plants and algae)**: For all scenarios, the LOC for exposure to octhilinone was not exceeded for the acute exposure to freshwater plants (Table 9, Table 10 and Table 11, Appendix 1).

## 5.0 Value

### 5.1 Effectiveness Against Pests

Efficacy data were provided from two commercial field trials that tested the ability of wood samples to resist mildew. The wood samples were treated with a range of concentrations of octhilinone (125, 250 and 375 ppm) added to the treatment tank prior to the wood treatments with copper azole. The trials were conducted on relevant commercial Canadian wood species in lumber yards at two different geographic sites in both Eastern and Western Canada. The trials were of appropriate experimental design containing control boards with no copper azole treatment to which Thor Acticide 45 Mildewcide was added and control boards with a copper azole treatment to which Thor Acticide 45 Mildewcide was added. At regular intervals the boards were assessed for the number of boards with mold and mildew growth and the percent area covered by mold and mildew growth. The data demonstrated that 250 ppm octhilinone added directly to the copper azole solution prior to treatment, provided effective protection to the treated wood against mildew growth on the wood surface.

### 5.2 Non-Safety Adverse Effects

No non-safety adverse effects associated with the use of Thor Acticide 45 Mildewcide as a mildewcide treatment for wood freshly treated with copper azole preservative were noted.

### 5.3 Consideration of Benefits

There is a significant mold and mildew growth problem on wood that has been freshly treated with wood preservatives, largely due to the commercial practice of tightly stacking the treated wood while still wet and wrapping with plastic prior to shipping and storage. Thor Acticide 45 Mildewcide provides a new active ingredient as a mildewcide for freshly treated wood, and the only one specifically for the protection of wood treated with copper azole.

#### 5.3.1 Social and Economic Impact

Due to negative consumer perceptions regarding mold and mildew, wood with mildew growing on the surface may be of decreased value or unmarketable.

#### 5.3.2 Survey of Alternatives

There is one combination of active ingredients currently registered as a mildewcide for wood that has been freshly treated with a heavy-duty wood preservative. However, this product is limited for use on wood treated with either chromated copper arsenate (CCA) or ammoniacal copper quat (ACQ) heavy-duty wood preservatives (see Table 14 of Appendix I). Thor Acticide 45 Mildewcide provides the only end-use product for the protection of wood treated with copper azole.

#### 5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

The development of resistance to octhilinone in mold and mildew growing on treated wood has not been reported and is unlikely to occur.

### 5.4 Supported Uses

The use of Thor Acticide 45 Mildewcide as a mildewcide on wood freshly treated with copper azole type heavy-duty wood preservatives has been supported at rates of up to 250 ppm active ingredient (see Table 15 of Appendix I).

## 6.0 Pest Control Product Policy Considerations

### 6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, octhilinone and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[9] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Octhilinone does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table 9 for comparison with Track 1 criteria.
- Transformation products do not meet all Track 1 criteria.

### 6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[10]. The list is used as described in the PMRA Notice of Intent NOI2005-01[11] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[12], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Octhilinone does not contain any formulants of health or environmental concern identified in the *Canada Gazette*.
- The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[13].

## 7.0 Summary

### 7.1 Human Health and Safety

The toxicology database submitted for octhilinone is adequate to define the majority of toxic effects that may result from exposure. In short- and long-term studies on laboratory animals, the primary effects noted were reductions in body weight, body weight gain, and food consumption as well as irritation at the site of application (skin, stomach or upper respiratory tract) and dermal sensitization. Octhilinone was not considered to have carcinogenic potential and was not considered

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9 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

10 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

11 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

12 DIR2006-02, *PMRA Formulants Policy.*

13 DIR2006-02, *PMRA Formulants Policy.*

to be genotoxic. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Effects on the developing young animal were observed at dose levels that were toxic to the mother. There was no effect on reproductive performance or outcome; however, effects on certain female reproductive parameters (decreased ovarian weights, changes in vaginal epithelium, increased primordial follicles) were observed. There was no indication that octhilinone targeted the immune or nervous systems.

Workers treating wood with Thor Acticide 45 Mildewcide and handling treated wood are not expected to be exposed to levels of octhilinone that will result in health risks of concern when the Thor Acticide 45 Mildewcide is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

Residential exposure to individuals handling and contacting wood is not expected to result in health risks of concern when Thor Acticide 45 Mildewcide is used according to label directions.

### 7.2 Environmental Risk

Octhilinone is not expected to be persistent in soils and aquatic systems. Octhilinone has a low potential to leach into ground water. As octhilinone is used in treated wood, however, it may be subject to leaching directly into surface water (in-service wood) or movement to aquatic systems via surface runoff (in-service wood and treatment facilities). An environmental assessment concluded that the risk to non-target organisms from the use of octhilinone as a heavy duty wood preservative is acceptable. Mitigation measures include the use of precautionary label statements identifying environmental hazards on the product labels, as well as directions to prevent surface runoff water from wood freshly treated with octhilinone to reach aquatic systems and to prevent the use of treated wood near marine and estuarine environments.

### 7.3 Value

The data submitted in support of Thor Acticide 45 Mildewcide were adequate to demonstrate efficacy in controlling mildew on wood treated with copper azole-type heavy duty wood preservatives. Thor Acticide 45 Mildewcide was effective in preventing mold and mildew growth on the freshly treated and wrapped wood over the entire test period when added to the copper azole treating solution at a rate of 250 ppm octhilinone. While there are mildewcides currently registered for this use, they are limited to wood treated with other heavy-duty wood preservative systems. Thor Acticide 45 Mildewcide will be the only mildewcide registered specifically for copper azole-treated wood. Furthermore, Thor Acticide 45 Mildewcide will be a new active ingredient for this type of use.

## 8.0 Proposed Regulatory Decision

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Acticide OIT Technical Industrial Microbicide and Thor Acticide 45 Mildewcide, containing the technical grade active ingredient octhilinone, to provide protection of freshly treated wood against mold and mildew growth for a period of several months.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

**Human Health**

Because there is a concern with users coming into direct contact with octhilinone on the skin or through inhalation, workers must wear full-face protection, chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gauntlets (long sleeved gloves), socks and chemical-resistant footwear when handling the concentrate or dilute solution, when opening treating cylinder doors, and during cleaning, maintenance and repair activities on storage vessels and treating cylinders. In addition, workers must wear a respirator with a NIOSH-approved organic vapour-removing cartridge with a prefilter approved for pesticides or, a NIOSH-approved canister approved for pesticides, when handling the concentrate, when handling the dilute solution in poorly ventilated areas, when opening treating cylinder doors and during cleaning, maintenance and repair activities on storage vessels or treating cylinders. Workers must wear chemical-resistant coveralls over long-sleeved shirt and long pants, goggles or face shield, chemical-resistant gauntlets, and chemical-resistant footwear when there is a potential of getting wet by the preservative solution, when moving loads and handling freshly treated wood. For other activities that involve working under dry conditions, a long-sleeved shirt, long pants, chemical-resistant gloves, chemical goggles and chemical-resistant footwear are required.

**Environment**

To protect sensitive aquatic species, precautionary label statements identifying environmental hazards and preventing the use of treated wood in and near marine/estuarine environments are required on the product labels.

## List of Abbreviations

| | |
|---|---|
| µg | micrograms |
| a.i. | active ingredient |
| ACQ | ammoniacal copper quat |
| AD | administered dose |
| ADI | acceptable daily intake |
| ALS | acetolactate synthase |
| ARfD | acute reference dose |
| bw | body weight |
| CAS | Chemical Abstracts Service |
| CCA | chromated copper arsenate |
| DNA | deoxyribonucleic acid |
| $DT_{50}$ | dissipation time 50% (the dose required to observe a 50% decline in concentration) |
| EEC | expected environmental concentration |
| $EC_{50}$ | effective concentration on 50% of the population |
| $ER_{25}$ | effective rate for 25% of the population |
| g | gram |
| HPLC | high performance liquid chromatography |
| IOM | Institute of Occupational Medicine |
| IUPAC | International Union of Pure and Applied Chemistry |
| kg | kilogram |
| $K_{oc}$ | organic-carbon partition coefficient |
| $K_{ow}$ | *n*–octanol-water partition coefficient |
| L | litre |
| $LC_{50}$ | lethal concentration 50% |
| $LD_{50}$ | lethal dose 50% |
| LOAEL | lowest observed adverse effect level |
| LOC | level of concern |
| LOEC | low observed effect concentration |
| LOQ | limit of quantitation |
| mg | milligram |
| mL | millilitre |
| MAS | maximum average score |
| MOE | margin of exposure |
| MS | mass spectrometry |
| N/A | not applicable |
| NOAEL | no observed adverse effect level |
| NOEC | no observed effect concentration |
| NOEL | no observed effect level |
| OC | organic carbon content |
| p*K*a | dissociation constant |
| PMRA | Pest Management Regulatory Agency |
| PPE | personal protective equipment |
| ppm | parts per million |
| PUF | polyurethane foam cylinder |
| SR | surface residue concentration |

| | |
|---|---|
| $t_{1/2}$ | half-life |
| TRR | total radioactive residue |
| TSMP | Toxic Substances Management Policy |
| USEPA | United States Environmental Protection Agency |
| UV | ultraviolet |

# Appendix I Tables and Figures

## Table 1 Residue Analysis

| Matrix | Analyte | Method Type | LOQ | Reference |
|---|---|---|---|---|
| Fish | Active | HPLC-MS | 0.01 mg/kg | 2150230 |
| Soil/sediment | Active | HPLC-MS | 0.01 mg/kg | 2150228 |
| Water | Active | HPLC-MS | 0.1 µg/L | 2150229 |

## Table 2 Toxicity Profile of Thor Acticide 45 Mildewcide Containing Octhilinone

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute Oral<br><br>Rat (Sprague Dawley)<br><br>PMRA 893238 | $LD_{50}$ = 279 mg/kg bw<br><br>High toxicity |
| Acute Dermal<br><br>Rat (Sprague Dawley)<br><br>PMRA 893239 | $LD_{50}$ > 2000 mg/kg bw<br><br>Low toxicity |
| Acute Inhalation<br><br>Rat (Sprague Dawley)<br><br>PMRA 893240 | $LC_{50}$ = 0.60 mg/L<br><br>Slight toxicity |
| Eye Irritation<br><br>PMRA 893241, 1018243 | Waiver rationale accepted on the basis of results from study conducted with a similar product.<br><br>Corrosive to eyes |
| Dermal Irritation<br><br>Rabbit (New Zealand White)<br><br>PMRA 893242 | MAS (24, 48, 72 hours) = 6.28<br>MIS = 6.33 recorded at 24, 48, 72, 96 hours<br><br>Severely irritating |
| Dermal Sensitization (Maximization)<br><br>Guinea pig (Dunkin/Hartley)<br><br>PMRA 893243 | Positive following challenge with 0.5% and 1% dilutions<br><br>Potential dermal sensitizer |

**Table 3 Toxicity Profile of Technical Octhilinone**

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Toxicokinetics<br><br>Rat (Wistar)<br><br>PMRA 2249344, 224934 | There were no significant differences in metabolic profiles between sexes, or between single and repeated low dosing scenarios.<br><br>Absorption was estimated to be 66% (single low dose) to 75% (single high dose) of the administered dose (AD). Absorption was rapid following a single low dose (Tmax = 1 hour) and slower following a single high dose (Tmax = 8-24 hours). Cmax was 3-5-fold higher following a single high dose compared to Cmax determined following a lower (by 10-fold) dose.<br><br>Excretion occurred primarily via the urine (44-51% of the AD), following by the fecal (23-29% of the AD) and biliary (19-20% of the AD) routes. Excretion was mostly complete within 24 hours of administration of the low dose, but was slower in high dose animals (mostly complete within 48 hours post-dosing).<br><br>Very little radioactivity (less than 3% of the AD) was retained in tissues up to 96 hours post-dosing. The radioactivity was widely distributed, with highest levels in liver and kidney.<br><br>Metabolism was extensive, with no parent compound detected in urine, bile or feces. Four major (>5% of the AD) and six minor metabolites were identified in urine, two major and two minor metabolites were identified in feces, and four minor metabolites were identified in bile.<br><br>Biotransformation involved cleavage of the isothiazolinone ring primarily via nucleophilic attack of the sulfur-nitrogen bond and consequent loss of the S-atom; oxidation at the isothiazolinone ring, either at the sulfur atom or at the double bond, or within the n-octyl chain; truncation at the alkyl chain. Phase II metabolism was observed as glucuronidation, glutathione conjugation and N-acetylation. |
| Acute Oral (Acute Toxic Class)<br><br>Rat (Wistar)<br><br>PMRA 1261638 | $LD_{50}$ = 500 – 2000 mg/kg bw<br><br>Moderate toxicity |
| Acute Oral<br><br>Rat (Sprague Dawley)<br><br>PMRA 1232251 | $LD_{50}$ (♂) = 708 mg/kg bw<br>$LD_{50}$ (♀) = 562 mg/kg bw<br><br>Moderate toxicity |
| Acute Oral<br><br>Rat (Sprague Dawley)<br><br>PMRA 1232250 | $LD_{50}$ (♂) = 794 mg/kg bw<br>$LD_{50}$ (♀) = 681 mg/kg bw<br><br>Moderate toxicity |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Acute Oral<br><br>Rabbit (New Zealand White)<br><br>PMRA 1232252 | $LD_{50}$ (♀) = 316 mg/kg bw<br><br>High toxicity |
| Acute Dermal<br><br>Rabbit (New Zealand White)<br><br>PMRA 1232250, 1240141 | $LD_{50}$ = 1.78 mL/kg (1636 mg/kg bw)<br><br>Slight toxicity |
| Acute Inhalation<br><br>Rat (Sprague Dawley)<br><br>PMRA 1213891 | $LC_{50}$ = 0.58 mg/L<br><br>Slight toxicity |
| Skin Irritation<br><br>PMRA 1334749 | Waiver rationale accepted on the basis of the corrosive nature of the technical grade active ingredient.<br><br>Corrosive to skin |
| Eye Irritation<br><br>Rabbit (New Zealand White)<br><br>PMRA 1232250 | Moderate to severe corneal opacity, iritis, marked conjunctival redness or blanching, moderate to severe chemosis, discharge. Irritation persisted to day 7 (study termination).<br><br>Corrosive to eyes |
| Dermal Sensitization (LLNA)<br><br>Mouse (CBA)<br><br>PMRA 1261637 | Positive<br><br>$EC_3$ = 0.46% (w/v)<br><br>Potential dermal sensitizer |
| Dermal Sensitization (modified Landsteiner method)<br><br>Guinea pig (English Shorthair)<br><br>PMRA 1240145 | Negative<br><br>Study was considered supplemental, non-guideline. |
| Dermal Sensitization (modified Buehler)<br><br>Guinea pig (Hartley)<br><br>PMRA 1213893 | Positive<br><br>$EC_{50}$ for induction calculated to be 0.013%<br>$EC_{50}$ for elicitation at induction concentration of 0.05% calculated to be 0.04%.<br><br>Potential dermal sensitizer |
| Dermal Sensitization (Repeated Insult Patch Test & Vapour Exposure Test)<br><br>Human<br><br>PMRA 1232256 | Positive following repeated insult with 1% dilution and after areas of skin were exposed to vapours generated from test material maintained in a warm water bath<br><br>Evidence of dermal sensitization<br><br>Study was considered supplemental. |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Dermal Sensitization (Repeated Insult Patch Test)<br><br>Human<br><br>PMRA 1232110, 1232111 | Negative following exposure to cloth treated with 10 or 50 ppm octhilinone.<br><br>Study was considered supplemental. |
| 14-day dermal (dose range-finding study)<br><br>Rat (Sprague Dawley)<br><br>PMRA 1261646 | NOAEL/LOAEL not established as study was considered supplemental.<br><br>Adverse effects at ≥ 100 mg/kg bw/day included dermal irritation (erythema, edema, atonia, desquamation, scabbing); ↓ bw, ↓ bwg week 2 (♂). |
| 90-day dermal<br><br>Rat (Sprague Dawley)<br><br>PMRA 1261641 | NOAEL for irritation = 5 mg/kg bw/day<br>LOAEL for irritation = 25 mg/kg bw/day, based on erythema, edema, atonia, slight to moderate squamous cell hyperplasia, moderate sebaceous cell hyperplasia, dermatitis.<br><br>NOAEL for systemic toxicity = 25 mg/kg bw/day<br>LOAEL for systemic toxicity = 125 mg/kg bw/day, based on ↓ bw, ↓ bwg (♂); ↑ adrenal gland wt, ↑ heart wt (♀). |
| 90-day dermal<br><br>Rat (Sprague Dawley)<br><br>Not in PMRA database; information based on USEPA RED (PMRA 2249337) | NOAEL for irritation not established as signs of irritation were observed down to the lowest dose tested.<br>LOAEL for irritation = 2.97 mg/kg bw/day, based on hyperkeratosis, acanthosis, foci of necrosis, eschar formation, sebaceous gland hyperplasia, chronic inflammation.<br><br>NOAEL for systemic toxicity = 5.95 mg/kg bw/day<br>LOAEL for systemic toxicity = 14.87 mg/kg bw/day, based on ↓ bwg (♂); ↓ HGB, HCT, RBC, albumin, glucose, protein (♀). |
| 90-day inhalation<br><br>Rat (Sprague Dawley)<br><br>PMRA 1141899 | NOAEC = 0.64 mg/m$^3$ (0.17 mg/kg bw/day)<br>LOAEC = 6.39 mg/m$^3$ (1.67 mg/kg bw/day), based on ↓ bw, ↓ bwg, rales, thriftless appearance, red stains on drop sheet, nasal cavity lesions (minimal to mild focal squamous metaplasia, minimal to mild acute inflammation, purulent exudate, secretory cell hyperplasia, eosinophilic staining of intraepithelial droplets); fluid in uterus, dyspnea (♀). |
| 90-day inhalation<br><br>PMRA 2249335 | Waiver rationale based on low potential for inhalation and read-across to 90-day inhalation study with ISL and IST (Kathon 886). |
| 90-day inhalation with Kathon 886 (3.5% ISL & 10.6% IST)<br><br>Rat (Sprague Dawley)<br><br>PMRA 1792779 | NOAEC = 0.34 mg/m$^3$ (0.09 mg/kg bw/day)<br>LOAEC = 1.15 mg/m$^3$ (0.30 mg/kg bw/day), based on very slight to slight rhinitis in nasal cavity. |
| 90-day oral (dietary)<br><br>Rat (Wistar)<br><br>PMRA 1401574 | NOAEL = 48/58 mg/kg bw/day in ♂/♀ (1000 ppm)<br>LOAEL = 203/249 mg/kg bw/day (3000 ppm), based on ↓ bw, ↓ bwg, hunched posture, abdominal swelling, piloerection, thickened limiting ridge and irregular surface of the forestomach, hyperplasia/hyperkeratosis of the squamous epithelium of the forestomach; ↓ fc week 1 (♂); 1 death day 76 (♀). |
| 90-day oral (dietary)<br><br>Dog (Beagle)<br><br>PMRA 1401577 | NOAEL = 119/141 mg/kg bw/day in ♂/♀<br>LOAEL not established as no adverse treatment-related effects were observed up to the highest dose tested. |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Chronic Toxicity/Carcinogenicity<br><br>PMRA 2249338 | Waiver rationale accepted based on the fact that the major toxicity observed in the database is irritation/corrosion at the site of primary contact, and that none of the studies demonstrated significant systemic toxicity. In addition, a 2-year drinking water study in rats with ISL/IST (Kathon 886) was cited as support for the waiver rationale. |
| 2-year oral (drinking water) with Kathon 886 (3.5% ISL & 10.6% IST)<br><br>Rat (Sprague Dawley)<br><br>PMRA 1631270 | NOAEL = 2.0/3.1 mg/kg bw/day in ♂/♀ (30 ppm)<br>LOAEL = 6.6/9.8 mg/kg bw/day in ♂/♀ (100 ppm), based on ↑ urinary specific gravity (secondary to ↓ water intake), dark foci/areas and depressed foci/areas in the gastric mucosa, prominent limiting ridge and/or thickened non-glandular mucosa of the forestomach, hyperplasia/hyperkeratosis of the squamous mucosa of the forestomach, focal necrosis of the glandular mucosa; ↓ bw, ↓ bwg, ↓ fc (♀).<br><br>No evidence of carcinogenicity |
| 2-Generation Reproductive Toxicity (dietary)<br><br>Rat (Wistar)<br><br>PMRA 2150226 | Parental NOAEL = 44/50 mg/kg bw/day in ♂/♀ (800 ppm)<br>Parental LOAEL = 104/114 mg/kg bw/day in ♂/♀ (1500 ppm), based on ↓ fc week 1 (P), irregular surface of forestomach corresponding to diffuse hyperplasia/hyperkeratosis (P&F1); ↓ bw & bwg premating (P), ↓ seminal vesicle wt (P), ↑ rel. kidney wt (F1), thickened limiting ridge of stomach (P&F1) (♂); ↑ fc during gestation (P), ↓ bw during lactation (P), ↓ spleen wt (P&F1), ↑ adrenal wt (P), ↓ thyroid wt (F1) (♀).<br><br>Reproductive NOAEL (♂) = 104 mg/kg bw/day (1500 ppm)<br>Reproductive LOAEL (♂) not established as no treatment-related effects on reproductive parameters were observed up to the highest dose tested.<br><br>Reproductive NOAEL (♀) could not be established due to missing evaluations of vaginal histology and ovarian follicle counts at the low and mid dose levels.<br>Reproductive LOAEL (♀) = 114 mg/kg bw/day (1500 ppm), based on ↓ ovarian wt (P&F1), ↓ uterine wt (P&F1), epithelial mucification of vagina (F1; delayed return to normal cyclical epithelium – not assessed at lower dose levels), ↑ primordial follicles (only assessed in F1; not assessed at lower dose levels).<br><br>Offspring NOAEL = 44/50 mg/kg bw/day in ♂/♀ (800 ppm)<br>Offspring LOAEL = 104/114 mg/kg bw/day in ♂/♀ (1500 ppm), based on ↓ bw LD 14 & 21 (F1&F2), ↓ spleen wt (F1&F2), ↓ abs thymus wt (F1&F2), ↓ rel thymus wt (F1 ♀).<br><br>No evidence of sensitivity of the young |
| Developmental toxicity (gavage) – dose range-finding study in non-pregnant female rats<br><br>Rat (Sprague Dawley)<br><br>PMRA 1261647 | NOAEL/LOAEL not established as study was considered supplemental.<br><br>Adverse effects noted in non-pregnant female rats at ≥ 10 mg/kg bw/day included salivation shortly after dosing, abnormal position, prominent lobular pattern in liver. |
| Developmental toxicity (gavage)<br><br>Rat (Sprague Dawley)<br><br>PMRA 1261644 | Maternal NOAEL = 60 mg/kg bw/day<br>Maternal LOAEL not established as no adverse effects were observed up to the highest dose tested.<br><br>Developmental NOAEL = 60 mg/kg bw/day<br>Developmental LOAEL not established as not treatment-related effects were observed up to the highest dose tested.<br><br>No evidence of sensitivity of the young |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Developmental toxicity (gavage)<br><br>Rat (Sprague Dawley)<br><br>PMRA 1141900 | Maternal NOAEL = 5 mg/kg bw/day<br>Maternal LOAEL = 30 mg/kg bw/day, based on 1 death, salivation, ↓ bw & bwg, ↓ corrected bw & bwg, ↓ fc.<br><br>Developmental NOAEL = 30 mg/kg bw/day<br>Developmental LOAEL not established as no treatment-related effects were observed up to the highest dose tested.<br><br>No evidence of sensitivity of the young |
| Developmental Toxicity (gavage)<br><br>Rabbit (New Zealand White)<br><br>PMRA 1141901 | Maternal NOAEL = 20 mg/kg bw/day<br>Maternal LOAEL = 80 mg/kg bw/day, based on clinical signs (anorexia, scant/soft/no feces), ↓ bw & bwg, bw loss during dosing, ↑ abortions, 1 death.<br><br>Developmental NOAEL = 20 mg/kg bw/day<br>Developmental LOAEL = 80 mg/kg bw/day, based on ↓ fetal bw.<br><br>No evidence of sensitivity of the young |
| Gene mutations in bacteria (Ames test)<br><br>*S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA102<br><br>PMRA 1261645 | Negative<br><br>Tested up to toxic concentrations.<br><br>Limitations with positive controls (in the presence of metabolic activation, only tested in TA98 and TA100); however study still considered acceptable as adequacy of S9 mix tested in other strain in quality control tests. |
| Gene mutations in bacteria (Ames test)<br><br>*S. typhimurium* strains TA98, TA100, TA1535, TA1537<br><br>PMRA 1141908 | Negative in the presence of metabolic activation.<br><br>Tested up to toxic concentrations.<br><br>Lack of adequate positive controls in assays without activation. |
| Gene mutations in mammalian cells *in vitro*<br><br>Chinese hamster ovary cells<br><br>PMRA 1141903 | Negative<br><br>Tested up to toxic concentrations. |
| Gene mutations in mammalian cells *in vitro*<br><br>Mouse lymphoma L5178Y cells<br><br>PMRA 1261643 | Negative<br><br>Tested up to toxic concentrations. |
| Mammalian chromosome aberration *in vitro*<br><br>Human lymphocytes<br><br>PMRA 1261639 | Negative<br><br>Study considered supplemental as testing was not conducted up to toxic or precipitating concentrations. |

| Study Type/Animal/PMRA # | Study Results |
|---|---|
| Mammalian chromosome aberration *in vitro*<br><br>Chinese hamster ovary cells<br><br>PMRA 1141904 | Positive<br><br>Increase in chromosome aberrations observed at concentrations that elicited cellular toxicity. |
| Mammalian chromosomal aberrations *in vivo* (gavage)<br><br>Rat (Sprague Dawley)<br><br>PMRA 1141906 | Negative<br><br>Study considered supplemental as examination was limited to slides from the high dose group. |
| Micronucleus assay in mammalian erythrocytes *in vivo* (gavage)<br><br>Mouse (CD-1)<br><br>PMRA 1261642 | Negative<br><br>650 mg/kg bw/day: two animals died, hunched gait, greasy fur, sunken eyes. |
| Unscheduled DNA synthesis in mammalian cells *in vivo/in vitro* (gavage)<br><br>Rat (Wistar)<br><br>PMRA 1261640 | Negative<br><br>≥ 250 mg/kg bw: 9 spontaneous activity, abdominal position, ruffled fur, apathy, closed eyelids |
| Unscheduled DNA synthesis in mammalian cells *in vitro* (gavage)<br><br>Rat hepatocytes<br><br>PMRA 1141907 | Negative<br><br>Tested up to toxic concentrations. |
| Oral Dose Range-Finding Study in Dogs<br><br>Dog (Beagle)<br><br>PMRA 1232253 | Dogs dosed with 100 mg/kg bw via capsule exhibited emesis and heavy defecation shortly after dosing. Dogs dosed with 500 mg/kg bw via gavage exhibited emesis shortly after dosing. A dietary concentration of 2000 ppm was accepted, whereas a dietary concentration of 10,000 ppm dietary was refused. |
| Upper Airway Irritation Potential<br><br>Mouse (Swiss-Webster)<br><br>PMRA 1157811 | $RD_{50}$ (concentration to produce 50% decrease in respiratory rate) = 19.9 µg/L<br><br>Study was considered supplemental, non-guideline. |
| Development and validation of an analytical method for the analysis of OIT in Altromin pellet rat and dog diet<br><br>PMRA 2249348 | Recovery of OIT from diet is concentration dependent, with lower recovery of test material from diets with lower target concentrations (for example, ~30% at 100 ppm, ~50% at 300 ppm, ~ 70% at 1000 ppm, ~90% at 3000 ppm).<br><br>It was concluded that the lower recoveries were most likely due to reaction of OIT with sulfur containing compounds in the diet and/or effects of irreversible binding of OIT. |

**Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Octhilinone**

| Exposure Scenario | Study | Point of Departure and Endpoint | Target MOE |
|---|---|---|---|
| Short- to intermediate-term dermal | 90-day dermal toxicity study in rats | NOAEL for systemic toxicity = 25 mg/kg bw/day, based on decreased body weight and body weight gain in males and increased adrenal gland and heart weight in females | 100 |
| Long-term dermal | 90-day dermal toxicity study in rats | NOAEL for systemic toxicity = 25 mg/kg bw/day, based on decreased body weight and body weight gain in males and increased adrenal gland and heart weight in females | 300[a] |
| Long-term inhalation | 90-day inhalation toxicity study in rats | NOAEC = 0.64 mg/m$^3$ (0.17 mg/kg bw/day), based on decreased body weight and body weight gain, clinical signs, and nasal cavity lesions | 300[a] |
| Non-dietary oral ingestion (short- to intermediate-term) | Developmental toxicity study in rats | NOAEL for maternal toxicity = 5 mg/kg bw/day, based on decreased body weight and body weight gain, salivation and one death | 100 |
| Dermal sensitization | local lymph node assay study in mice | $EC_3$ = 0.46% (230 µg/cm$^2$) | 100 |
| Cancer | A cancer risk assessment was not required | | |

[a] Includes a 3-fold factor to extrapolate from a short-term to a long-term exposure scenario

**Table 5 Fate and behaviour in the terrestrial and aquatic environments**

| Study type | Test material | Study conditions | Value or Endpoint | Classification/ Interpretation | Major transformation products | References[1] (PMRA #) |
|---|---|---|---|---|---|---|
| **Abiotic transformation** | | | | | | |
| Hydrolysis | Octhilinone | 30d, pH 5, 7, and 9 at 25°C | Stable | Limited susceptibility to hydrolysis at relevant pH (5-9) | NA | 2177119 |
| Phototransformation - soil | Octhilinone | Dry soil, continuous lightning at 42.3W/m$^2$ | $DT_{50}$=13.1d | Not a major route of transformation | NA | 1401581 |

| Study type | Test material | Study conditions | Value or Endpoint | Classification/ Interpretation | Major transformation products | References[1] (PMRA #) |
|---|---|---|---|---|---|---|
| Phototransformation - water | Octhilinone | pH 7 buffer, sterile, continuous lightning at 42.2W/$m^2$ | $DT_{50}$=1.8d | Not expected to be a major route of transformation | N-(N-octyl) acetamide; N-(N-octyl) ethyl amine M7[2] | 1401583 |
| | Octhilinone | Natural pond water, sterile, continuous lightning at 42.2W/$m^2$ | $DT_{50}$=2.5d | Not expected to be a major route of transformation | N-(N-octyl) acetamide; M7[2] M10[2] | |
| | N-(N-octyl) acetamide | pH 7 buffer, sterile, continuous lightning at 42.2W/$m^2$ | $DT_{50}$=2.0d | Not expected to be a major route of transformation | NA | |
| | N-(N-octyl) acetamide | Natural pond water, sterile, continuous lightning at 42.2W/$m^2$ | $DT_{50}$=3.3d | Not expected to be a major route of transformation | NA | |
| Phototransformation - air | Octhilinone | AOPWIN (continuous illumination) | DT50=0.14d | Not expected to be subject to long range transport | NA | 1401584 |
| **Biotransformation** | | | | | | |
| Soil -aerobic | Octhilinone | 100d, three soils; pH 5.7-6.9, %OC 0.95-2.29, 20 and 6°C | $DT_{50}$=0.4d to 4d | Non-persistent | $CO_2$ | 1401585 |
| Water -aerobic | Octhilinone | 29d, river water, 10 and 100°g/L, 20°C; pH 8.04, %OC 5.16 | T½=0.6-1.2d | Non-persistent | $CO_2$ | 1401586 |
| | Octhilinone | 17d, sea water, 10 and 100°g/L, 20°C; pH 8.16, %OC 1.22 | T½=1.6-2.1d | Non-persistent | $CO_2$ | 1401587 |
| **Mobility** | | | | | | |
| Adsorption/desorption | Octhilinone | Three soils (pH 6.0-7.4, 0.12-1.1%OC) | Koc=497 to 1 162 | Low mobility | NA | 2257178 |
| Adsorption | Octhilinone | Sewage sludge, %O.C. 31.6% | Koc=6740 | Low mobility | NA | 2249350 |
| Leaching from wood | Octhilinone | 14 days, 0.4$cm^2_{wood}/cm^3_{water}$, 0.08-0.24kg/$m^3$, 22°C | 31.2-36.2% leached Maximum flux of 120 $mg_{a.i.}\,d^{-1}$ over the first 6 hours. | | NA | 1401614 2150320 |
| | Octhilinone | 19 days, 0.06kg/$m^3$, 0.4$cm^2_{wood}/cm^3_{water}$, 8 days of simulated rainfall (2x60min/d) | 27.5% leached | | NA | 2249383 |

| Study type | Test material | Study conditions | Value or Endpoint | Classification/ Interpretation | Major transformation products | References[1] (PMRA #) |
|---|---|---|---|---|---|---|
| Volatilization | Octhilinone | 24h, soil, water, wood | Does not volatilize | | NA | 1401591<br>1401589<br>1401590 |
| **Bioconcentration/Bioaccumulation** | | | | | | |
| Bioconcentration | Octhilinone | 0.10 and 0.48µg/L | BCF=405-629 (whole fish) | not bioaccumulative | NA | 1401594 |

[1]USEPA classification, where applicable
[2]M7and M10 are unknown multiple component transformation products.

## Table 6 Toxicity to non-target species

| Organism | Study type | Species | Test material | Endpoint | Value | Classification[1] | Reference (PMRA #) |
|---|---|---|---|---|---|---|---|
| **Terrestrial species** | | | | | | | |
| Birds | Acute oral | Bobwhite quail (*Colinus virginianus*) | Octhilinone | $LD_{50}$ | 346 $mg_{a.i.}/kg$ | Moderately toxic | 1232126 |
| | Dietary | Bobwhite quail (*Colinus virginianus*) | Octhilinone | 8-d $LC_{50}$ | > 3267 $mg_{a.i.}/kg_{diet}$ | Slightly toxic to non-toxic | 1142169 |
| | | Mallard duck (*Anas platyrhynchos*) | Octhilinone | 8-d $LC_{50}$ | 1215 $mg_{a.i.}/kg_{diet}$ | Slightly toxic | 1142170 |
| Mammals | Acute oral | Rat | Octhilinone | $LD_{50}$ (♂)<br>$LD_{50}$ (♀) | 794 $mg_{a.i.}/kg_{bw}$<br>681 $mg_{a.i.}/kg_{bw}$ | Moderately toxic | 1232250 |
| | | | End-use product | $LD_{50}$ | 279 $mg_{a.i.}/kg_{bw}$ | Highly toxic | 893238 |
| **Freshwater Organisms** | | | | | | | |
| Invertebrates | Acute | *Daphnia magna* | Octhilinone | 48-h $EC_{50}$ | 0.18 $mg_{a.i.}/L$ | Highly toxic | 1232129 |
| | Chronic | *Daphnia magna* | Octhilinone | 21-d NOEC | 0.0016 $mg_{a.i.}/L$ | Very highly toxic | 2177121 |
| | | | | 21-d LOEC | 0.0032 $mg_{a.i.}/L$ | | |
| Fish | Acute | Rainbow trout (*Oncorkynchus mykiss*) | Octhilinone | 96-h $LC_{50}$ | 0.036 $mg_{a.i.}/L$ | Very highly toxic | 1018234 |
| | | Bluegill sunfish (*Lepomis macrochirus*) | Octhilinone | 96-h $LC_{50}$ | 0.16 $mg_{a.i.}/L$ | Highly toxic | 2177123 |
| Algae | Acute | Green alga (*Scenedesmus subspicatus*) | Octhilinone | 72-h $E_rC_{50}$ | 0.084 $mg_{a.i.}/L$ | | 893177 |
| | | | | 72-h $E_bC_{50}$ | 0.031 $mg_{a.i.}/L$ | | |
| Vascular plants | | *Lemna gibba* | Octhilinone | 7-d $EC_{50}$ | 0.14 $mg_{a.i.}/L$ | | 1401597 |
| **Marine Organisms** | | | | | | | |
| Crustacean | Acute | Mysid shrimp (*Mysidopsis bahia*) | Octhilinone | 96-h $LC_{50}$ | 0.071 $mg_{a.i.}/L$ | Very highly toxic | 1142177 |
| Fish | Acute | Sheepshead minnow (*Cyprinodon variegatus*) | Octhilinone | 96-h $LC_{50}$ | 0.16 $mg_{a.i.}/L$ | Highly toxic | 1142175 |
| Algae | Acute | Marine algae (*Skeletonema Costatum*) | Octhilinone | 72-h $E_rC_{50}$ | 0.0016 $mg_{a.i.}/L$ | | 1401596 |
| | | | | 72-h $E_bC_{50}$ | 0.0011 $mg_{a.i.}/L$ | | |
| | | | | 72-h $E_vC_{50}$ | 0.0012 $mg_{a.i.}/L$ | | |

[1]USEPA classification, where applicable

## Table 7 Scenarios considered for the risk assessment

| Scenario | Description | Details | |
|---|---|---|---|
| **Scenario for industrial preventive treatment** | | | |
| 1 | ***Runoff from storage of treated wood*** | | |
| | ***After vacuum pressure process*** | Surface area of the storage place:<br>Exposed surface of wood:<br>Duration of storage:<br>Rain fraction reaching water:<br>Flow rate of creek/river: | 525 $m^2$<br>11 $m^2_{wood}/m^2_{storage\ area}$<br>35 d<br>0.5<br>0.3 $m^3s^{-1}$ |

| Scenario | Description | Details | |
|---|---|---|---|
| | *After double vacuum/ low pressure process* | Surface area of the storage place: | 262.5 $m^2$ |
| | | Exposed surface of wood: | 11 $m^2_{wood}/m^2_{storage\ area}$ |
| | | Duration of storage: | 35 d |
| | | Rain fraction reaching water: | 0.5 |
| | | Flow rate of creek/river: | 0.3 $m^3s^{-1}$ |
| **Scenarios for treated wood in service** | | | |
| 2 | *Generic freshwater environment* | | |
| | *Amphibians compartment*<br>Bridge, walkway or dock;<br>over a shallow pond or lake. | Wooden structure size: | 1.2m × 4m |
| | | Leachable wood surface area: | 10.36 $m^2$ |
| | | Body of water: | 194 $m^3$ |
| | | Ratio wood area: wood volume: | 54 $m^2m^{-3}$ |
| | | Ratio wood area: water volume: | 0.05 $m^2m^{-3}$ |
| | *Other organisms compartment*<br>Bridge, walkway or dock;<br>over a pond or lake. | Wooden structure size: | 1.2m × 4m |
| | | Leachable wood surface area: | 10.36 $m^2$ |
| | | Body of water: | 1 036 $m^3$ |
| | | Ratio wood area: wood volume: | 54 $m^2m^{-3}$ |
| | | Ratio wood area: water volume: | 0.01 $m^2m^{-3}$ |
| 3 | *Aquatic exposure from runoff*<br>Runoff from decks and fences | Wooden structure size (deck): | 6m × 3.7m |
| | | Wooden structure size (fence): | 30.5m × 1.8m |
| | | Leachable wood surface area: | 77.1 $m^2$ |
| | | Body of water: | 1 036 $m^3$ |
| | | Fraction reaching water: | 0.5 |
| | | Ratio wood area: wood volume: | 40 $m^2m^{-3}$ |
| | | Ratio wood area: water volume: | 0.07 $m^2m^{-3}$ |

## Table 8 Flux of active ingredient from freshly treated wood exposed to water as a function of time

| Time (d) | FLUX(Δt) ($mg_{a.i}\ m^{-2}d^{-1}$) |
|---|---|
| 0.25 | 120.0 |
| 1 | 43.1 |
| 2 | 27.7 |
| 4 | 16.2 |
| 6 | 13.9 |
| 8 | 10.4 |
| 10 | 9.2 |
| 12 | 9.2 |
| 14 | 8.1 |

## Table 9 EECs in aquatic compartments for the different scenarios considered in the risk assessment

| Scenario | Description | EECs[1] (mg/L) | | | Time to Max[4] |
|---|---|---|---|---|---|
| | | First day[2] | Longer term[3] | Maximum | (d) |
| **Scenario for industrial preventive treatment** | | | | | |
| 1[5] | *Runoff from storage of treated wood* | | | | |
| | *After vacuum pressure process* | 0.0013 | - | 0.0013 | - |
| | *After double vacuum/ low pressure process* | 0.0006 | - | 0.0006 | - |

| Scenario | Description | EECs[1] (mg/L) | | | Time to Max[4] |
|---|---|---|---|---|---|
| | | First day[2] | Longer term[3] | Maximum | (d) |
| **Scenarios for treated wood in service** | | | | | |
| 2 | ***Generic freshwater environment*** | | | | |
| | ***Amphibians compartment*** Bridge, walkway or dock; over a shallow pond or lake. | 0.003 | 0.001 | 0.003 | 2 |
| | ***Other organisms compartment*** Bridge, walkway or dock; over a pond or lake. | 0.0005 | 0.0002 | 0.0006 | 2 |
| 3 | ***Aquatic exposure from runoff*** Runoff from decks and fences | 0.002 | 0.001 | 0.002 | 2 |

[1]Expected Environmental Concentration (EEC) based on the scenario parameters as listed in Table 3. A dissipation half-life of 1.2 d in freshwater environments and of 2.1 d in estuarine/marine environments were considered, based on aquatic biotransformation of the active ingredient. From laboratory leaching data and assuming a steady flux of active ingredient of 8.1 $mg_{a.i.}m^{-2}d^{-1}$ from day 14 after installation/immersion of the wooden structure (Table 4):
EEC = Flux * exposed surface of wood * surface area of the storage place * rain fraction reaching water / flow rate
[2] EEC 24 hours after installation/immersion of the wooden structure.
[3] EECs 14 days after installation/immersion of the wooden structure and up until all active ingredient is expected to have leached, based on retention of 0.17 $kg_{a.i.}/m^3$ (equivalent to a solution retention of 674 $L/m^3$ containing 250 ppm Acticide 45); EECs were calculated on a day-by-day basis and were found to be equivalent when rounded to a single digit. The active ingredient is expected to have completely leached after 374, 512 and 2 555 days after installation/immersion for scenario 2, 3 and 4, respectively.
[4] Number of days after installation/immersion of the wooden structure required to reach the maximum EEC.
[5] Emissions from a storage facility are considered stable over time and are calculated from the average daily flux of 11.25 $mg_{a.i.}m^{-2}d^{-1}$ calculated for the storage period.

## Table 10 Expected environmental concentrations (EECs) and risk quotients (RQs) for freshwater organisms based on Scenario 1, Storage of Treated Wood (surface runoff from treatment facility).

| Organism | Endpoint[1] | | | | | EEC[2] ($mg_{a.i.}/L$) | RQ[3] |
|---|---|---|---|---|---|---|---|
| ***Storage after vacuum pressure process*** | | | | | | | |
| Daphnia magna | 1/2 | 48-h EC50 | = | 0.09 | $mg_{a.i.}/L$ | 0.0013 | 0.01 |
| | | 21-d NOEC | = | 0.0016 | $mg_{a.i.}/L$ | 0.0013 | 0.8 |
| Rainbow trout | 1/10 | 96-h LC50 | = | 0.0036 | $mg_{a.i.}/L$ | 0.0013 | 0.4 |
| Bluegill sunfish | 1/10 | 96-h LC50 | = | 0.016 | $mg_{a.i.}/L$ | 0.0013 | 0.08 |
| Green alga | 1/2 | 72-h $E_bC50$ | = | 0.0155 | $mg_{a.i.}/L$ | 0.0013 | 0.08 |
| Vascular plant | 1/2 | 7-d EC50 | = | 0.07 | $mg_{a.i.}/L$ | 0.0013 | 0.02 |
| ***Storage after double vacuum / low pressure process*** | | | | | | | |
| Daphnia magna | 1/2 | 48-h EC50 | = | 0.09 | $mg_{a.i.}/L$ | 0.0006 | 0.01 |
| | | 21-d NOEC | = | 0.0016 | $mg_{a.i.}/L$ | 0.0006 | 0.4 |
| Rainbow trout | 1/10 | 96-h LC50 | = | 0.0036 | $mg_{a.i.}/L$ | 0.0006 | 0.2 |
| Bluegill sunfish | 1/10 | 96-h LC50 | = | 0.016 | $mg_{a.i.}/L$ | 0.0006 | 0.04 |
| Green alga | 1/2 | 72-h $E_bC50$ | = | 0.0155 | $mg_{a.i.}/L$ | 0.0006 | 0.04 |
| Vascular plant | 1/2 | 7-d EC50 | = | 0.07 | $mg_{a.i.}/L$ | 0.0006 | 0.01 |

[1]Endpoints used in the acute exposure risk assessment are derived by dividing the $EC_{50}$ or $LC_{50}$ from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
[2]Expected Environmental Concentration (EEC) as reported in Table 5.
[3]Risk Quotient (RQ) = exposure/toxicity. RQ > 1 indicates exceedance of LOC (Level Of Concern).

**Table 11 Expected environmental concentrations (EECs) and risk quotients (RQ) for freshwater organisms based on Scenario 2, Generic Freshwater Environment (direct leaching into water from wood in service).**

| Organism | Endpoint[1] | | | | | $EEC_{max}$[2] ($mg_{a.i.}/L$) | Time to $EEC_{max}$ (d) | RQ[3] |
|---|---|---|---|---|---|---|---|---|
| Daphnia magna | 1/2 | 48-h EC50 | = | 0.09 | $mg_{a.i.}/L$ | 0.0006 | 2 | 0.01 |
| | | 21-d NOEC | = | 0.0016 | $mg_{a.i.}/L$ | 0.0006 | 2 | 0.4 |
| Amphibians (Rainbow trout) | 1/10 | 96-h LC50 | = | 0.0036 | $mg_{a.i.}/L$ | 0.003 | 2 | 0.8 |
| Rainbow trout | 1/10 | 96-h LC50 | = | 0.0036 | $mg_{a.i.}/L$ | 0.0006 | 2 | 0.2 |
| Bluegill sunfish | 1/10 | 96-h LC50 | = | 0.016 | $mg_{a.i.}/L$ | 0.0006 | 2 | 0.04 |
| Green alga | 1/2 | 72-h $E_bC50$ | = | 0.0155 | $mg_{a.i.}/L$ | 0.0006 | 2 | 0.04 |
| Vascular plant | 1/2 | 7-d EC50 | = | 0.07 | $mg_{a.i.}/L$ | 0.0006 | 2 | 0.04 |

[1]Endpoints used in the acute exposure risk assessment are derived by dividing the $EC_{50}$ or $LC_{50}$ from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
[2]Maximum Expected Environmental Concentration (EEC) as reported in Table 5.
[3]Risk Quotient (RQ) = exposure/toxicity. RQ > 1 indicates exceedance of LOC (Level Of Concern)

**Table 12 Expected environmental concentrations (EECs) and risk quotients (RQs) for freshwater organisms based on Scenario 3, Surface Runoff (wood in service; terrestrial uses).**

| Organism | Endpoint[1] | | | | | $EEC_{max}$[2] ($mg_{a.i.}/L$) | Time to $EEC_{max}$ (d) | RQ[3] | Days at RQ > 1[4] (d) |
|---|---|---|---|---|---|---|---|---|---|
| Daphnia magna | 1/2 | 48-h EC50 | = | 0.09 | $mg_{a.i.}/L$ | 0.002 | 2 | 0.02 | - |
| | | 21-d NOEC | = | 0.0016 | $mg_{a.i.}/L$ | 0.002 | 2 | **1.3** | 7 |
| Rainbow trout | 1/10 | 96-h LC50 | = | 0.0036 | $mg_{a.i.}/L$ | 0.002 | 2 | 0.6 | - |
| Bluegill sunfish | 1/10 | 96-h LC50 | = | 0.016 | $mg_{a.i.}/L$ | 0.002 | 2 | 0.1 | - |
| Green alga | 1/2 | 72-h $E_bC50$ | = | 0.0155 | $mg_{a.i.}/L$ | 0.002 | 2 | 0.14 | - |
| Vascular plant | 1/2 | 7-d EC50 | = | 0.07 | $mg_{a.i.}/L$ | 0.002 | 2 | 0.03 | - |
| *Bolded text indicates that the RQ exceeds the level of concern (LOC =1)* | | | | | | | | | |

[1]Endpoints used in the acute exposure risk assessment are derived by dividing the $EC_{50}$ or $LC_{50}$ from the appropriate laboratory study by a factor of two (2) for aquatic invertebrates and plants, and by a factor of ten (10) for fish and amphibians.
[2] Maximum Expected Environmental Concentration (EEC) as reported in Table 5.
[3] Risk Quotient (RQ) = exposure/toxicity. RQ > 1 indicates exceedance of LOC (Level Of Concern).
[4] Total number of days during which RQ is greater than 1.

## Table 13 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

| TSMP Track 1 Criteria | TSMP Track 1 Criterion value | | Active Ingredient Endpoints |
|---|---|---|---|
| Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1] | Yes | | Yes |
| Predominantly anthropogenic[2] | Yes | | Yes |
| Persistence[3] | Soil | Half-life ≥ 182 days | Half-life = 0.4-4 days |
| | Water | Half-life ≥ 182 days | Half-life = 0.6-2.1 days |
| | Sediment | Half-life ≥ 365 days | N/A |
| | Air | Half-life ≥ 2 days or evidence of long range transport | Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on volatilization study results. |
| Bioaccumulation[4] | Log $K_{OW}$ ≥ 5 | | 3.42 |
| | BCF ≥ 5000 | | 405-629 |
| | BAF ≥ 5000 | | Not available |
| Is the chemical a TSMP Track 1 substance (all four criteria must be met)? | | | No, does not meet TSMP Track 1 criteria. |

[1] All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the *Canadian Environmental Protection Act* toxicity criterion may be refined if required (that is, all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) then the criterion for persistence is considered to be met.

[4] Field data (for example, bioaccumulation factors [BAFs]) are preferred over laboratory data (for example, bioconcentration factors [BCFs]) which, in turn, are preferred over chemical properties (for example, *n*-octonol–water partition coefficient [log $K_{OW}$]).

## Table 14 Registered Alternatives (as of January 2014)

| Reg. No. | Product Name | Active Ingredient | Use Limitations |
|---|---|---|---|
| 24535 | Kathon 886F | 5-chloro-2-methyl-4-isothiazolin-3-one; 2-methyl-4-isothiazolin-3-one | For use on CCA-treated wood |
| 24624 | Arch Mold Inhibitor K-18500 | 5-chloro-2-methyl-4-isothiazolin-3-one; 2-methyl-4-isothiazolin-3-one | For use on CCA-treated wood |
| 25389 | Supatimber H.E. 14 Wood Mildewcide | 5-chloro-2-methyl-4-isothiazolin-3-one; 2-methyl-4-isothiazolin-3-one | For use on CCA-treated wood |
| 28013 | Acticide 14 | 5-chloro-2-methyl-4-isothiazolin-3-one; 2-methyl-4-isothiazolin-3-one | For use on CCA and ACQ-treated wood |
| 29516 | Acticide MV14 | 5-chloro-2-methyl-4-isothiazolin-3-one; 2-methyl-4-isothiazolin-3-one | For use on CCA-treated wood |

**Table 15 List of Supported Uses**

| Proposed label claim | Supported use claim |
|---|---|
| COPPER AZOLE-TREATED WOOD: Add up to 0.55 kg of ACTICIDE® 45 Mildewcide per 1000 litres of treating solution. This addition level will afford protection for 6 months. | Accepted as proposed |

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Chemistry

| PMRA Document Number | Reference |
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| 1476180 | 1999, Part 2.12.1 Establishing Certified Limits, DACO: 2.12.1 |
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| 1476264 | 1995, Product Identity and Composition of Acticide 45, DACO: 2.12.1 |
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| 1476508 | 1994, 61-2 Description of Begining Materials and Manufacturing Process., DACO: 2.11 |
| 1476517 | 1994, Process Diagram of Quality and Production Control for Acticide 45, DACO: 2.11.3 |
| 1476832 | 1994, Acticide 45 Attachment F Evolution of the Manufacturing Process at Thor, DACO: 2.11.3 |
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| 1476915 | 1994, Analysis and Certification of Product Ingredients of Acticide 45., DACO: 2.16 |
| 1476930 | 1994, Analytical Methods to Verify Certified Limits, DACO: 2.12.1 |
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| 1477142 | 1994, 1 Year Storage Stability of Acticide 45., DACO: 2.14.14 |
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| 2150230 | 2007, Development and Validation of a Residue Analytical Method for the Determination of OIT in Biota (fish), DACO: 8.2.2.4 |

## 2.0 Human and Animal Health

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| 893240 | 1992, Acticide 45 Acute Inhalation Toxicity Study in Rats 4-hour Exposure., DACO: 4.6.3 |
| 893241 | Primary Eye Irritation-Waiver., DACO: 4.6.4 |
| 893242 | 1991, Skin Irritation to The Rabbit of Acticide 45., DACO: 4.6.5 |
| 893243 | 1991, Skin Sensitization in the Guinea-Pig of Acticide 45. Huntington Research Centre Ltd. Thor GmbH. 91246D/THR 20/SS. GLP. Unpublished., DACO: 4.6.6 |
| 1018243 | 2005, Waiver in Support of Not Submitting an Eye Irritation Study., DACO: 4.6.4 |
| 1141899 | 1989. Skane M-8 HQ Micobicide - Thirteeen-week inhalation toxicity study in rats (87R-013;86P-196). June 29, 1989. DACO: 4.7 |
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| 1213893 | 1988. A study of the concentration-dependent delay contact hypersensitivity in guinea pigs (83R-143), DACO: 4.2.6 |
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| 1232111 | 1972. Dermal Hazards of Cloth Treated with RH-893 to Human Skin, DACO: 4.6.6 |
| 1232250 | 1970. Acute oral-Rats; Acute dermal-Rabbits; Acute eye irritaiton-Rabbit; Acute Inhalation-Rats, DACO: 4.2.1,4.2.2,4.2.3,4.2.4 |
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| 1232252 | 1971. Oral Dose Range - Rabbits, DACO: 4.2.1 |

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| 1232253 | 1971. Oral Dose Range and Acceptability Study - Dogs - RH-893 TECH, DACO: 4.2.1 |
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## B. Additional Information Considered

### i) Published Information

#### 1.0 Chemistry

#### 2.0 Human and Animal Health

| | |
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### ii) Unpublished Information

#### 1.0 Environment

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